Case Presentation :
An adolescent (21 year old) male patient with Tcell –ALL had Primary Induction Failure with Augmented BFM undergo Inotuzumab Ozogamicin Proceeded to HSCT

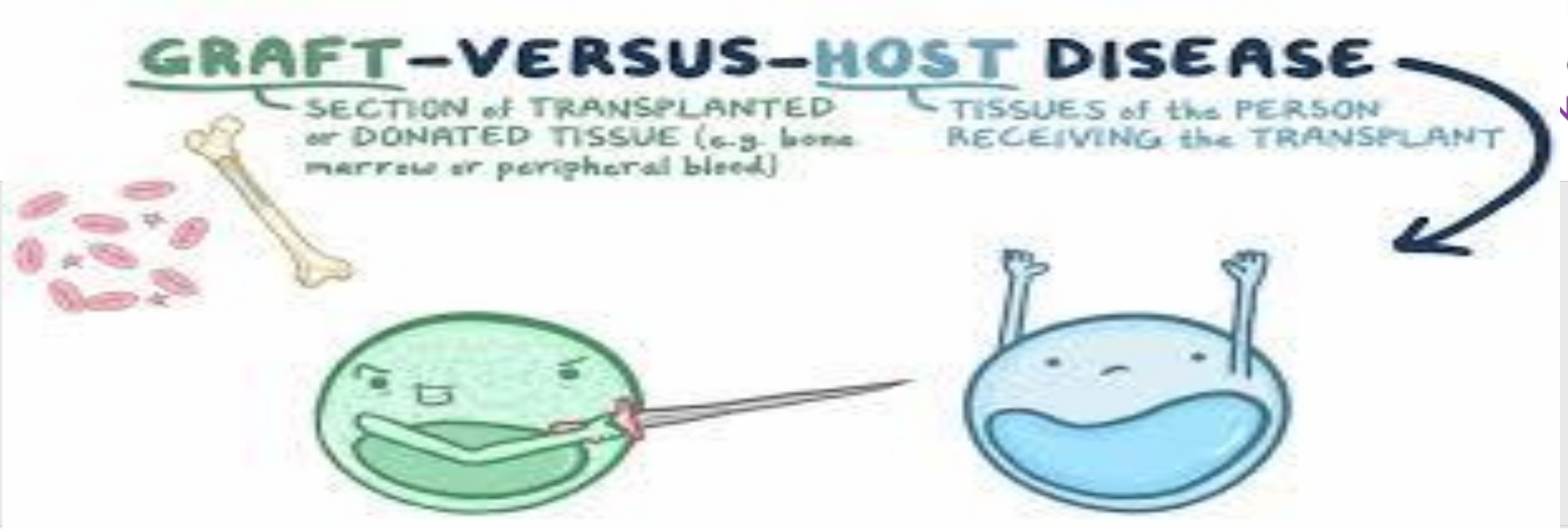
- **Allogeneic Hematopoietic Stem Cell Transplantation**
- **Mismatched Unrelated Donor (MMUD; 9/10 HLA-A Mismatch) HSCT(PBSC)**
- **Conditioning Regimen (MAC/ BuCy)**

Busulfan (Total dose : 12.8 mg/ kg body weight)
Cyclophosphamide (Total dose : 120 mg/ kg body weight)
Rabbit ATG (Thymoglobulin) (Total dose : 7.5 mg/ kg body weight) (Day -3 to -1)

GVHD prophylaxis with cyclospurine and methotrexate for. Day 11 methotrexate was 50% dose reduced, and leucovorin rescue was added for severe mucositis

GVHD Prophylaxis

Dr.Parkhide



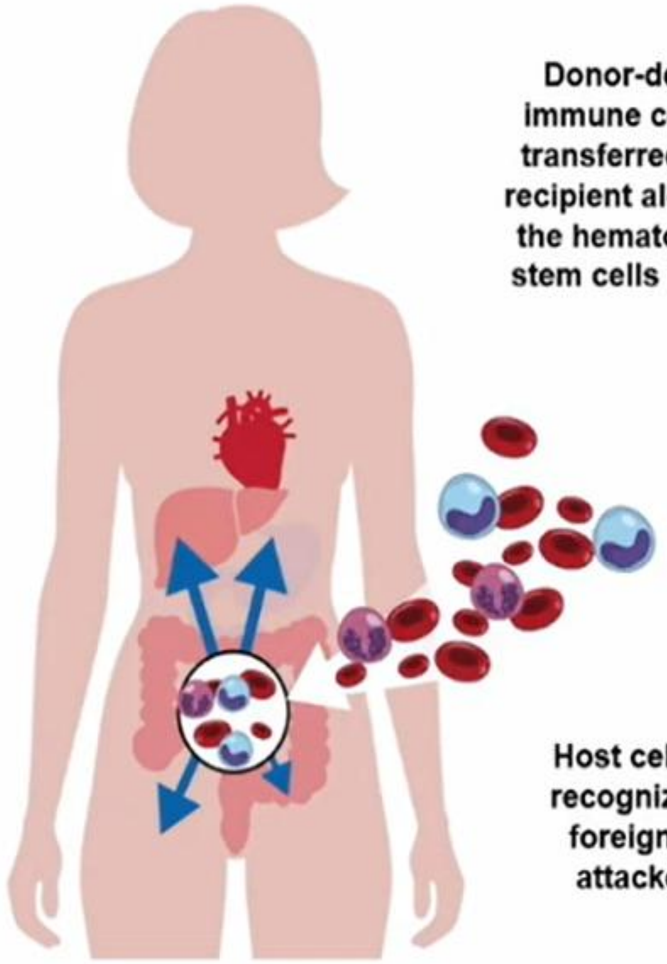
OPTIONS®
NCOLOGY

GVHD PROPHILAXIS

DR SAYRH PARKHIDEH

TALEGHANI HOSPITAL

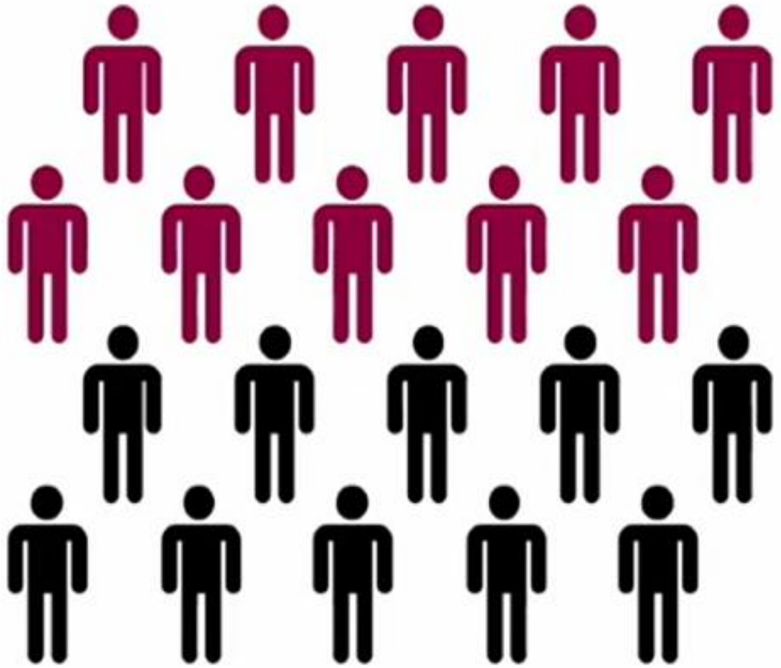
GvHD is a major complication of alloSCT



Donor-derived immune cells are transferred to the recipient along with the hematopoietic stem cells (graft)[1,2]

Host cells are recognized as foreign and attacked[1,2]

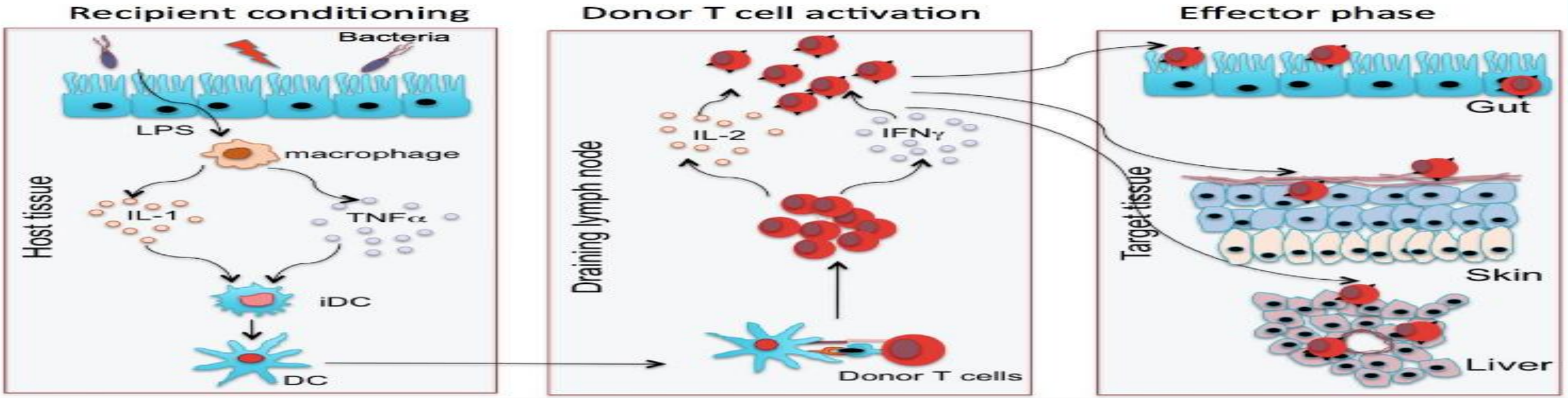
- Up to 50% of patients develop GvHD, despite immunosuppressive prophylaxis[3-5]



alloSCT, allogeneic stem cell transplant; GvHD, graft-versus-host disease.

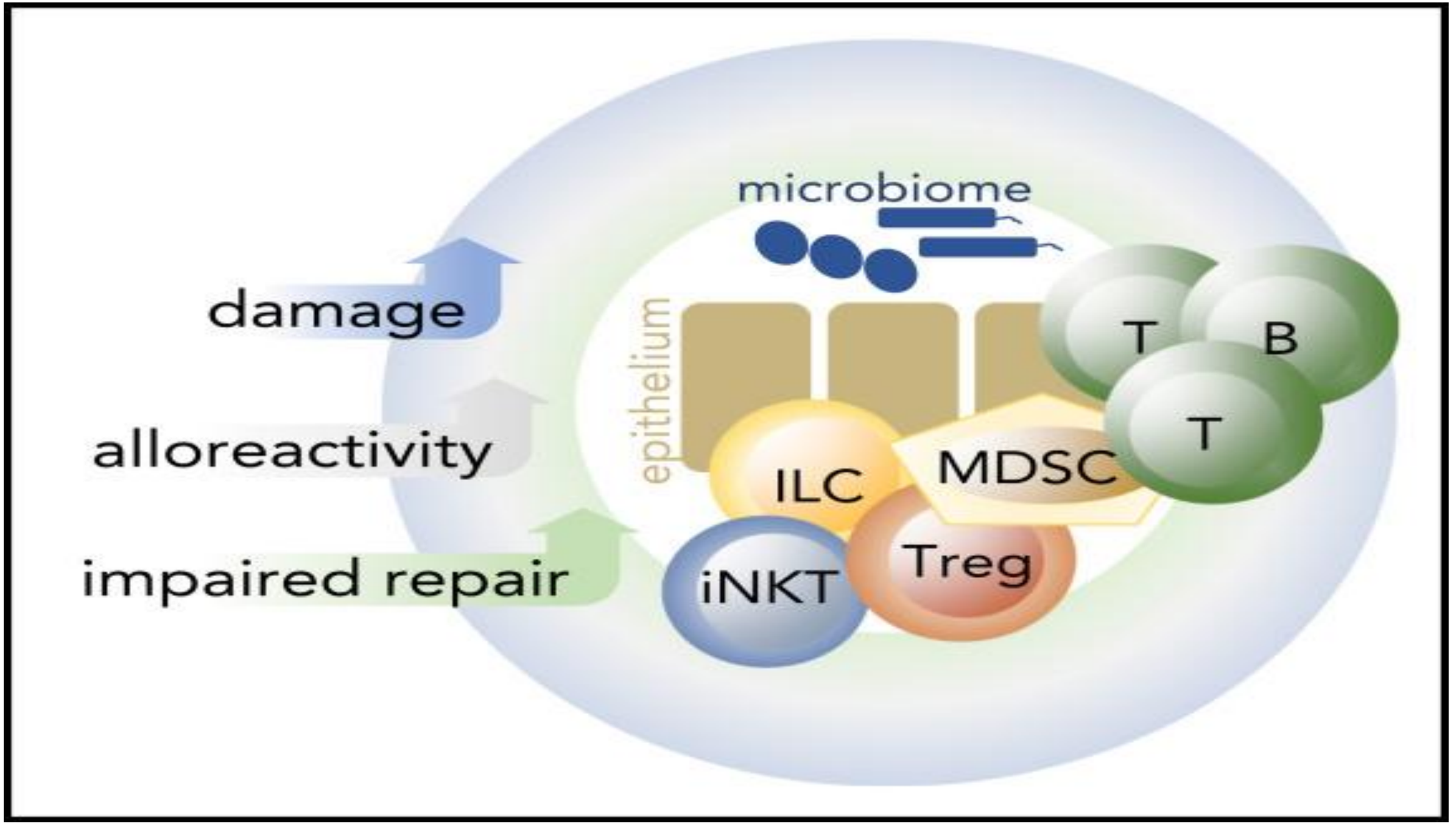
1. Ferrara JL, et al. Lancet. 2009;373:1550-61. 2. Spoerl S, et al. Blood. 2014;123:3832-42. 3. Zeiser R, Blazar BR. N Engl J Med. 2017;377:2167-79. 4. Jagasia M, et al. Immunotherapy. 2018;10:391-402. 5. Martin PJ, et al. Biol Blood Marrow Transplant. 2012;18:1150-63.

Pathophysiology of Graft versus Host Disease



Pathophysiology of aGvHD

Phase 1: recipient-conditioning tissue damage	Phase 2: donor T cell activation	Phase 3: target tissue destruction
• Conditioning regimens damage tissues	• Host APCs activate donor T cells	• T cells migrate to target tissues and cause tissue destruction
• Inflammatory cytokines, such as TNF-α, IL-1, and IL-6, are released	• T cells proliferate and differentiate into different subsets	• Th1 cells promote proliferation and differentiation of CTLs and stimulate NK cells, inducing apoptosis via effector molecules (e.g. perforin, granzymes, IFN-γ)
• Host APCs are activated		


damage
alloreactivity
impaired repair
microbiome
epithelium
T
B
T
ILC
MDSC
Treg
iNKT

Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria

Mary E. D. Flowers,[1,2] Yoshihiro Inamoto,[1] Paul A. Carpenter,[1,3] Stephanie J. Lee,[1,2] Hans-Peter Kiem,[1,2] Effie W. Petersdorf,[1,2] Shalini E. Pereira,[1] Richard A. Nash,[1,2] Marco Mielcarek,[1,2] Matthew L. Fero,[1,2] Edus H. Warren,[1,2] Jean E. Sanders,[1,3] Rainer F. Storb,[1,2] Frederick R. Appelbaum,[1,2] Barry E. Storer,[1,4] and Paul J. Martin[1,2]

[1]Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA; and Departments of [2]Medicine, [3]Pediatrics, and [4]Biostatistics, University of Washington School of Medicine, Seattle, WA

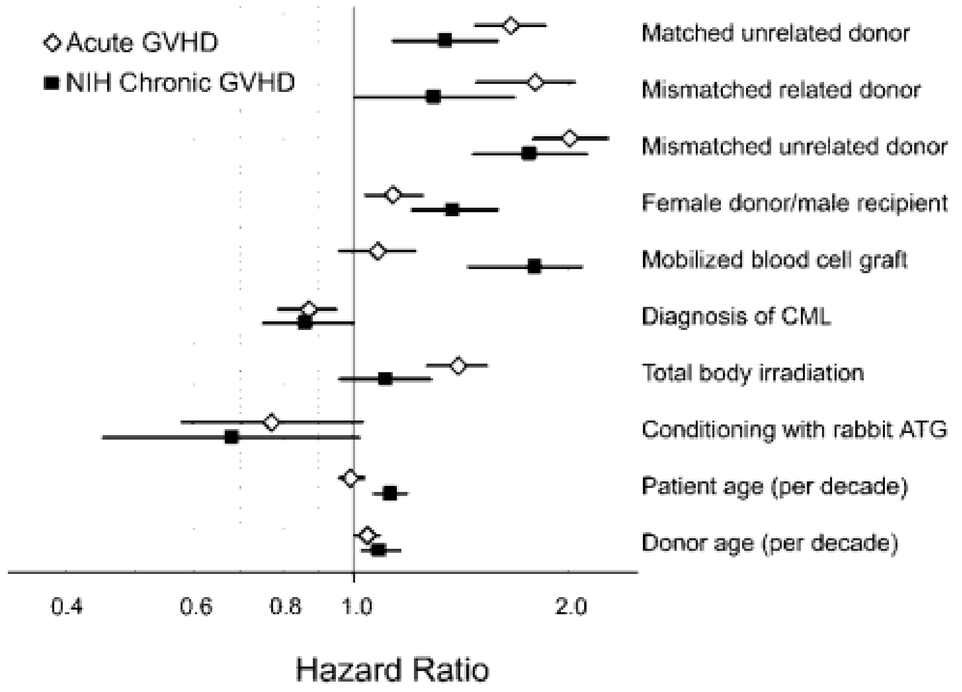
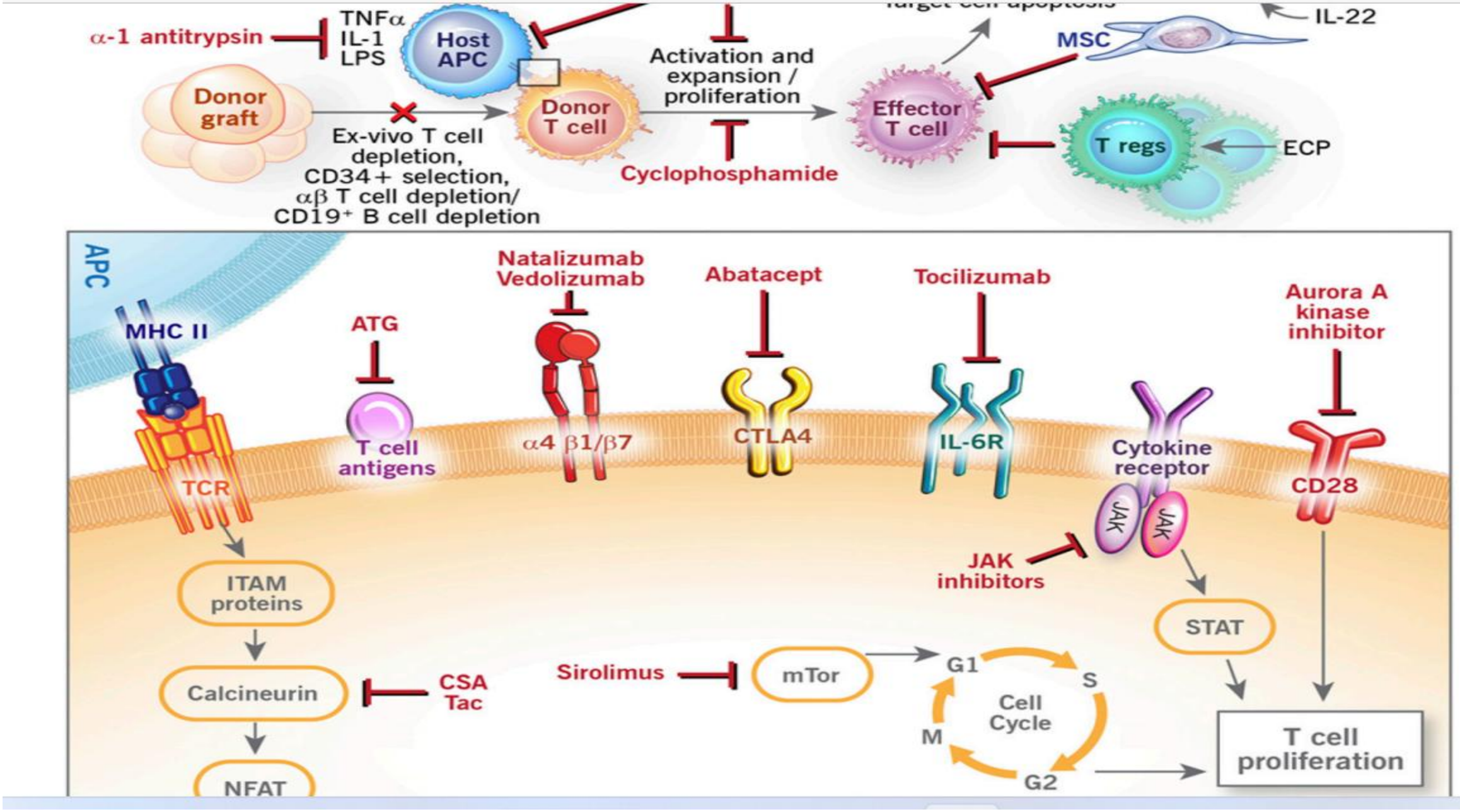


Figure 2. Multivariate risk factor profiles for grades 2-4 acute GVHD and NIH chronic GVHD. Hazard ratio and 95% CI for each risk factor are shown. The analysis included 2355 grades 2-4 acute GVHD events and 1022 NIH chronic GVHD events. Hazard ratios are relative to patients without the risk factor.

Table 3. Summary of factors associated with increased risk of grades 2-4 acute and chronic GVHD

	Acute GVHD		Chronic GVHD	
Factor	Previously reported*	Current study	Previously reported†	Current study‡
HLA mismatch or unrelated donor	yes	yes	yes	yes
Older patient age	yes	no	yes	yes
Older donor age	yes	yes	yes	yes
Female donor for male recipient	yes	yes	yes	yes
Parity of female donor (allosensitization)	yes	§	yes	§
Intensity of conditioning regimen	yes	‖	no	‖
Mobilized blood cell graft	no/yes	no	yes	yes
Donor lymphocyte infusion	yes	¶	yes	¶
Prior acute GVHD	n/a	n/a	yes	yes



- Calcineurin inhibitors (tacrolimus/Tac and cyclosporine/CyA) inhibit the proliferation and activation of Tcells and have been used in combination with either methotrexate (MTX) or mycophenolate mofetil (MMF) as standard prophylaxis in HLA-matched HSCT

- The combination of Tac/MTX was found to be significantly superior to CyA/MTX is the prevention of grade II-IV aGVHD and extensive chronic GVHD in HLA-matched sibling and unrelated donors, although a benefit in overall survival (OS) was not shown

- Therefore, both regimens are considered standard backbones to most GVHD prevention strategies for patients undergoing allogeneic HCT.

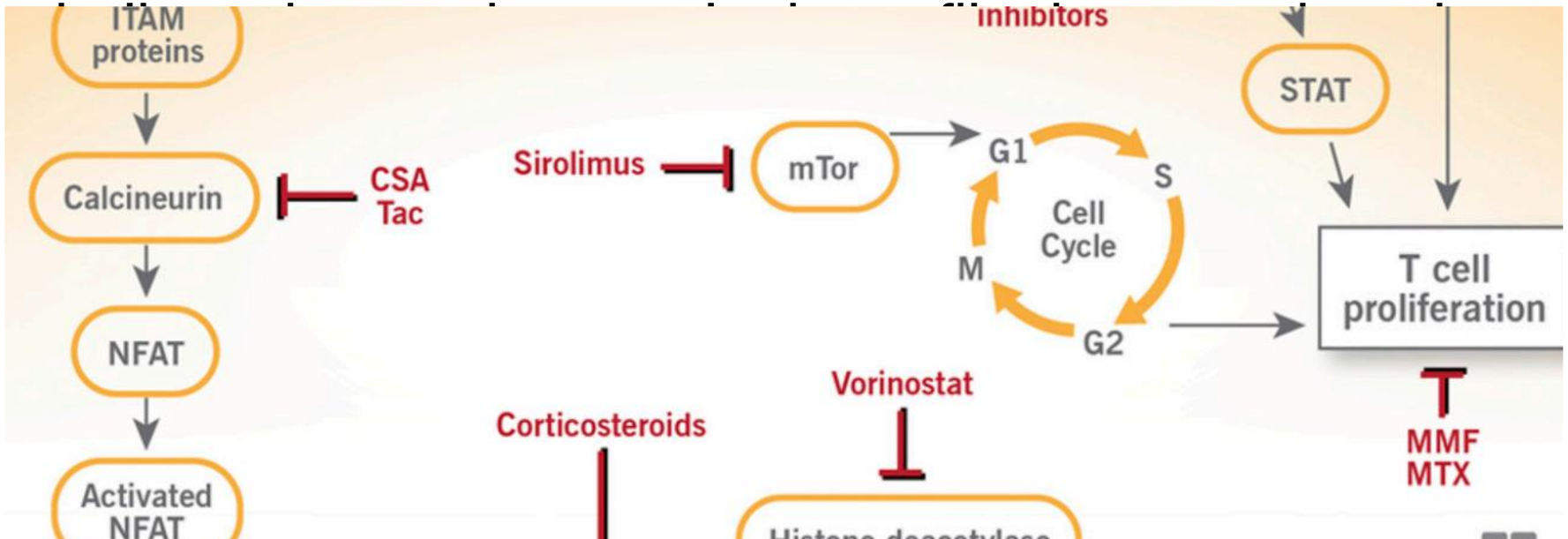
Mycophenolate mofetil (MMF)

- a selective inhibitor of inosine monophosphate dehydrogenase that is a key enzyme in the de novo synthesis of guanine nucleotides

- **A recent Center for International Blood and Marrow Transplant** Research study of **3979** matched sibling donors and **4163** unrelated donors showed significantly inferior GVHD and survival outcomes with CSA MMF compared with Tac , MTX, CSA , MTX, and Tac , MMF in **myeloablative transplantation**, suggesting an advantage of MTX over MMF for GVHD prevention.

- Sirolimus is a mTOR inhibitor which inhibits effector Tlymphocytes and in in-vitro studies appeared to spare regulatory T-lymphocytes.

- shown to be associated with better GVHD outcomes and hence be



- sirolimus in combination with tacrolimus was compared with the standard Tac/MTX platform.

- There was no difference in grades II-IV aGVHD and Cgvhd

- better grade III-IV aGVHD outcomes with sirolimus/Tac were seen

- Tac + sirolimus is thus considered an important alternative for **patients undergoing total body irradiation**-based transplantation, particularly for may be at higher risk for **developing severe mucositis** or **require faster engraftment for risk of infection**.

Translational Advances in GVHD Prophylaxis

- **In-vivo T-Cell Depletion/Modulation**
- Post-transplant Cyclophosphamide
- Anti-thymocyte Globulin

- **Ex-vivo T-Cell Depletion/Modulation**

"ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?"

Prof. Mohamad MOHTY
Clinical Hematology and Cellular Therapy Dpt.
Sorbonne University
Hôpital Saint-Antoine
Paris, France

ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?

Rationale for the Cyclophosphamide-Based Haplo Approach

- **Properties of post-transplantation Cy:**
  - **Selectively toxic to *proliferating*, alloreactive T cells over non-proliferating, non-alloreactive T cells** (*Fuchs EJ, et al. Bone Marrow Transplant. 2015;50 Suppl 2(0 2):S31-6.*)
  - **Non-toxic to hematopoietic stem cells** (*Ruggeri A, et al. Haematologica. 2017;102(2):401-410.*)
  - **Decreases acute GvHD in animal models** (*Luznik L, et al. Blood. 2001;98(12):3456-64.*)

Signatures of GVHD and relapse after posttransplant cyclophosphamide revealed by immune profiling and machine learning

Shannon R. McCurdy,[1,*] Vedran Radojcic,[2,3,*,†] Hua-Ling Tsai,[4] Ante Vulic,[5] Elizabeth Thompson,[5] Sanja Ivcevic,[2,3] Christopher G. Kanakry,[6] Jonathan D. Powell,[4] Brian Lohman,[3] Djamilatou Adom,[6] Sophie Paczesny,[7,8] Kenneth R. Cooke,[4] Richard J. Jones,[4] Ravi Varadhan,[5] Heather J. Symons,[4] and Leo Luznik[4,†]

Blood. 2022;139(4):608-623.

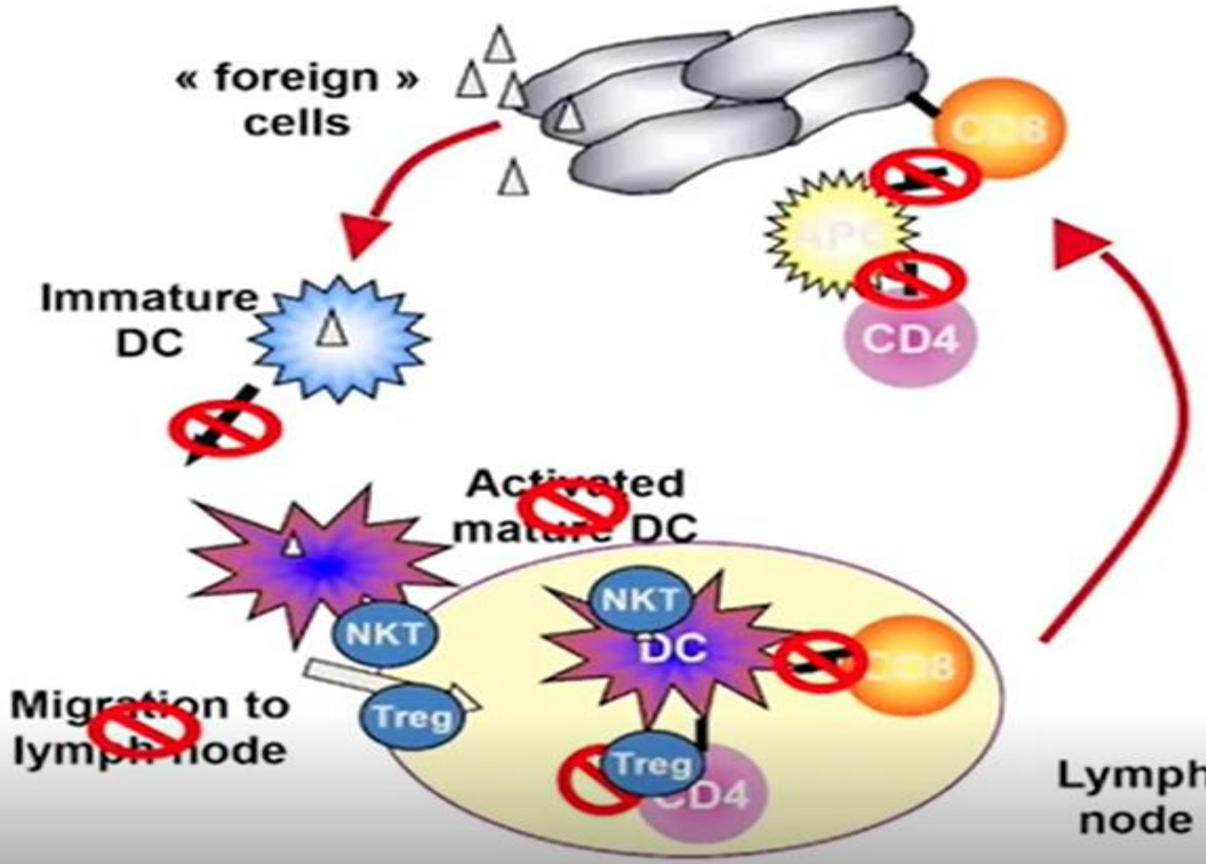
Cy: Cyclophosphamide. GvHD: Graft versus Host Disease.

ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?

Summary of rATG Mechanisms of Action

- The polyclonal nature of rATG is reflected in its diverse effects on the immune system :
  - T-cell depletion in blood and peripheral lymphoid tissues
  - Interference with leukocyte/endothelium interactions
  - Apoptosis in all B-cell lineages
  - Induction of Tregs/NKT cells

- → *rATG provides multifaceted immunomodulation*



TG: rabbit Antithymocyte Globulin. T reg: regulatory T cells. NKT: Natural Killer (NK) T cells.
PC: Antigen-Presenting Cell. DC: Dendritic Cell.

Adapted from Mohty M. Leukemia. 2007;21(7):1387-94.

Table 3. Randomized studies of rabbit ATG as GvHD prevention in patients given allogeneic hematopoietic cell transplantation.

	N. of patients	ATG brand / total dose (mg/kg)	Acute GvHD II-IV	Chronic GvHD	Non-relapse mortality	Relapse	Overall survival
			% ATG/ % no ATG (*P*)	% ATG/ % no ATG (*P*)	% ATG/ % no ATG (*P*)	% ATG/ % no ATG (*P*)	% ATG/ % no ATG (*P*)
Bacigalupo *et al.*[55]	54	T / 7.5	69 / 72 (0.6)	38 / 65 (0.08)	43 / 39 (0.7)[a]	10 / 12 (0.6)[a]	56 / 55 (0.8)[a]
Bacigalupo *et al.*[55]	55	T / 15	37 / 79 (0.001)	41 / 59 (0.3)	47 / 49 (0.9)[b]	36 / 18 (0.8)[b]	43 / 43 (0.8)[b]
Finke & Socie *et al.*[56 60]	201	F / 60	33 / 51 (0.01)	30 / 60 (<0.001)[a]	19 / 34 0.18)[a]	33 / 28 (0.5)[a]	55 / 43 (0.39)[a]
Kroger *et al.*[58]	155	F / 30	11 / 18 (0.13)	32 / 69 (<0.001)[c]	14 / 12 (0.6)[c]	32 / 26 (0.17)[c]	74 / 78 (0.5)[c]
Walker *et al.*[57]	196	T / 4.5	50 / 65 (0.01)[d]	22 / 33 (0.06)[b]	23 / 24 (NS)[b]	11 / 16 (NS)[b]	75 / 65 (0.24)[b]

[a]at 3 years; [b]at 1 year; [c]at 2 years; [d]grade I-IV at day 100. F: ATG-Fresenius; T: ATG-Thymoglobuline.

Table 4. Proposed indications for immunoregulation with ATG in patients given PBSC from allogeneic donors.

	Recommendation for ATG	Dose and timing of ATG
Myeloablative PBSCT from matched sibling donors[58]	standard of care	ATG-F 10 mg/kg/day on days -3, -2 and -1.
Myeloablative PBSCT from HLA-matchedunrelated donors[56,60,57]	standard of care	ATG-F 20 mg/kg/day on days -3, -2 and -1*. ATG-T 0.5 mg/kg on day -2 and 2 mg/kg on days -1 and +1.
RIC-PBSCT fludarabine-busulfan[68]	recommended	ATG-T 2.5 mg/kg/day on days -2 and -1.
Non-myeloablative PBSCT	developmental	/
HLA-haplo-identical stem cell transplantation (Bejing approach)[88]	standard of care	ATG-T 2.5 mg/kg/day from days -5 to -2.

* some centers use smaller doses such as 15 mg/kg total dose.

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Regular Article

TRANSPLANTATION

Posttransplant cyclophosphamide vs antithymocyte globulin in HLA-mismatched unrelated donor transplantation

Giorgia Battipaglia,[1,2] Myriam Labopin,[1,3,4] Nicolaus Kröger,[5] Antonin Vitek,[6] Boris Afanasyev,[7] Inken Hilgendorf,[8] Johannes Schetelig,[9] Arnold Ganser,[10] Didier Blaise,[11] Maija Itälä-Remes,[12] Jakob R. Passweg,[13] Francesca Bonifazi,[14] Jurgen Finke,[15] Annalisa Ruggeri,[16] Arnon Nagler,[3,17] and Mohamad Mohty[1,3,4]

blood® 12 SEPTEMBER 2019 | VOLUME 134, NUMBER 11

Retrospective study using the registry data of the ALWP of the EBMT to perform a matched-pair analysis comparing two strategies, PTCY versus ATG, in a 9/10 MMUD setting; 93 patients receiving PTCY were matched with 179 patients receiving ATG.

ATG: Antithymocyte Globulin. GvHD: Graft versus Host Disease. HLA: Human Leucocyte Antigen. PTCy: Post Transplant Cyclophosphamide. MMUD: Mismatched Unre

KEY POINTS

- **PTCY results in a lower incidence of severe acute GVHD compared with ATG in patients transplanted from 9/10 MMUD for acute myeloid leukemia.**
- **PTCY results in better survival compared with ATG in patients transplanted from 9/10 MMUD for acute myeloid leukemia.**

ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?

PTCy versus ATG after RIC allogeneic cell transplantation: conclusions

- The use of PTCY for GVHD prophylaxis resulted in similar outcomes compared to ATG in patients who underwent FB2 allogeneic stem cell transplantation with a 10/10 HLA-matched related or unrelated donor.
- Both PTCY or ATG can be used for GVHD prophylaxis in patients receiving FB2 conditioning prior to allogeneic stem cell transplantation with a 10/10 HLA-matched related or unrelated donor.

ATG: Antithymocyte Globulin. PTCy: Posttransplant Cyclophosphamide. RIC: Reduced Intensity Conditioning. FB2: fludarabine +2 days of busulfan at 3.2 mg/kg/d iv. GvHD: Graft versus Host Disease

Brissot E, et al. Presidential Symposium #GS2-2. Van Bekkum Award; EBMT 2021.

ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?

What's next ?

ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?

> Leuk Lymphoma. 2021 Dec;62(14):3373-3383. doi: 10.1080/10428194.2021.1966781.
Epub 2021 Aug 26.

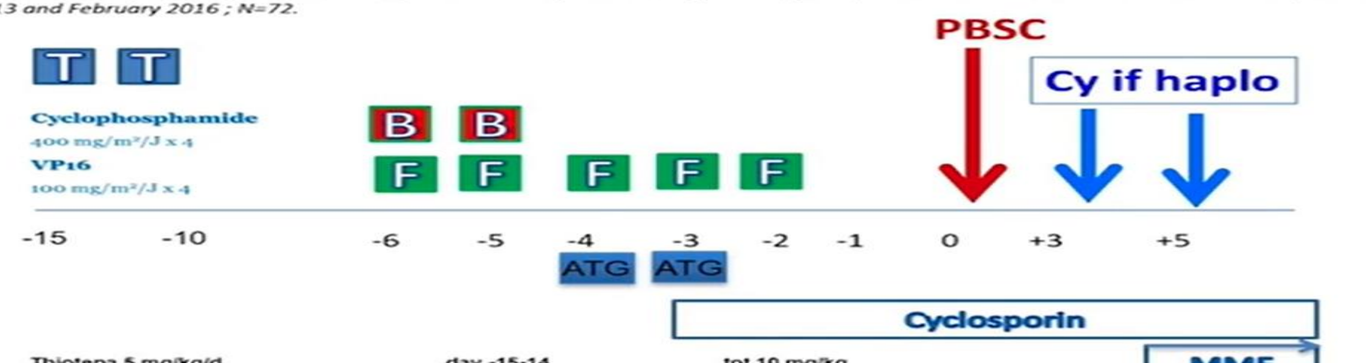
Lower dose of ATG combined with post-transplant cyclophosphamide for HLA matched RIC alloHCT is associated with effective control of GVHD and less viral infections

Maria Queralt Salas [1 2 3], Eshetu G Atenafu [4], Arjun Datt Law [1 2], Wilson Lam [1 2], Ivan Pasic [1 2], Carol Chen [2], Dennis Dong Hwan Kim [1 2], Fotios V Michelis [1 2], Armin Gerbitz [1 2], Jeffrey Howard Lipton [1 2], Jonas Mattsson [1 2], Rajat Kumar [1 2], Auro Viswabandya [1 2]

ersus post-transplant cyclophosphamide for GvHD prophylaxis

ATG *and* PtCy combination

Retrospective multicenter study including all consecutive patients with R/R hematological malignancy who underwent allo-SCT with TEC-RIC sequential conditioning between April 2013 and February 2016 ; N=72.



Thiotepa 5 mg/kg/d	day -15-14	tot 10 mg/kg
Cy 400 mg/m²/d	day -13 to -10	tot 1600 mg/m²
VP16 100 mg/m²/d	day -13 to -10	tot 400 mg/m²
Fludarabine 30 mg/m²/d	day -6-5-4-3-2	tot 150 mg/m²
Iv Busulfan 3.2 mg/kg/24h	day -6-5	tot 6.4 mg/kg
ATG 2.5 mg/Kg/24h	day -4-3	total 5 mg/kg

Cy: Cyclophosphamide. ATG: Anti-Thymocyte Globulin. PBSCs: Peripheral Blood Stem Cells. CsA: Cyclosporine A. MMF: Mycophenolate Mofetil. TEC-RIC: thiotepa, VP16, cyclophosphamide followed by fludarabine, intravenous busulfan and anti-thymocyte globulin.

Dulery R, *et al.* Biol Blood Marrow Transplant. 2018;24(5):1013-1021

ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?

ATG *and* PtCy Combination

Outcomes at Year 2	Total (n=72) n (%)	Haplo (n=27) n (%)	MRD (n=16) n (%)	UD (n=29) n (%)	p-value (comparison between Haplo, MRD & UD groups)
Relapse incidence	38.4	35.9	31.2	43.1	*P=0.858*
NRM	23.7	14.8	25	31	*P=0.376*
Acute GVHD II-IV	23.6	11.1	12.5	41.4	*P=0.027*
Chronic GVHD	32.1	30	37.5	31	*P=0.909*

Haplo: Haploidentical. MRD: Matched Related. NRM: Norrelapse Mortality. UD: Unrelated Donor.

Dulery R, *et al.* Biol Blood Marrow Transplant. 2018;24(5):1013-1021.

T-CELL DEPLETED HSCT

T-CELL REPLETED HSCT

GRAFT MANIPULATION	INFUSED CELLS	ADVANTAGES	DISADVANTAGES
CD34+ POSITIVE SELECTION	HSC	• Well estabilished approach • Negligible risk of GvHD • No need for post-transplant GvHD prophylaxis	• Delayed T-cell recovery • 6-8 weeks to obtain mature NK recovery • High rates of infectious complications and TRM
CD3+/CD19+ NEGATIVE SELECTION	HSC, NK	• Early NK-cell recovery • Low risk of post-transplant EBV- related lymphoproliferative disease	• Higher number of residual T cells compared to CD34+ cell positive selection • Need for post-transplant GvHD prophylaxis
TCRαβ+/CD19+ NEGATIVE SELECTION	HSC, T γδ, NK	• Early γδT- and NK-cell recovery • Anti-pathogen effect of NK-cells and γδ T-cells • Excellent platform for post-transplant cellular immunotherapies	• Few studies reported so far • Need for qualified personnel and equipped facility for graft manipulation

INFUSED CELLS	GvHD PROPHYLAXIS		
HSC, B, T γδ, T αβ, M, DC, NK	*POST-TRANSPLANT CY* *Selective depletion of alloreactive T cells*	• Presumed lower costs • No-need for graft manipulation	• Few studies reported so far • Inadequate control of alloreactivity in children under the age of 10 years
G-CSF PRIMING HSC, B, T γδ, T αβ, M, DC, NK	*MULTIAGENT PROPHYLAXIS* *Csa MMF MTX* *Non-selective T cell inhibition*	• Presumed lower costs • No-need for graft manipulation	• Few studies reported so far, limited to SAA patients • Higher risk of acute and chronic GvHD • Need for prolonged GvHD prophylaxis

Table 1. Clinical trials with TCR-αβ/CD19-depleted haematopoietic stem cells (HSCs).

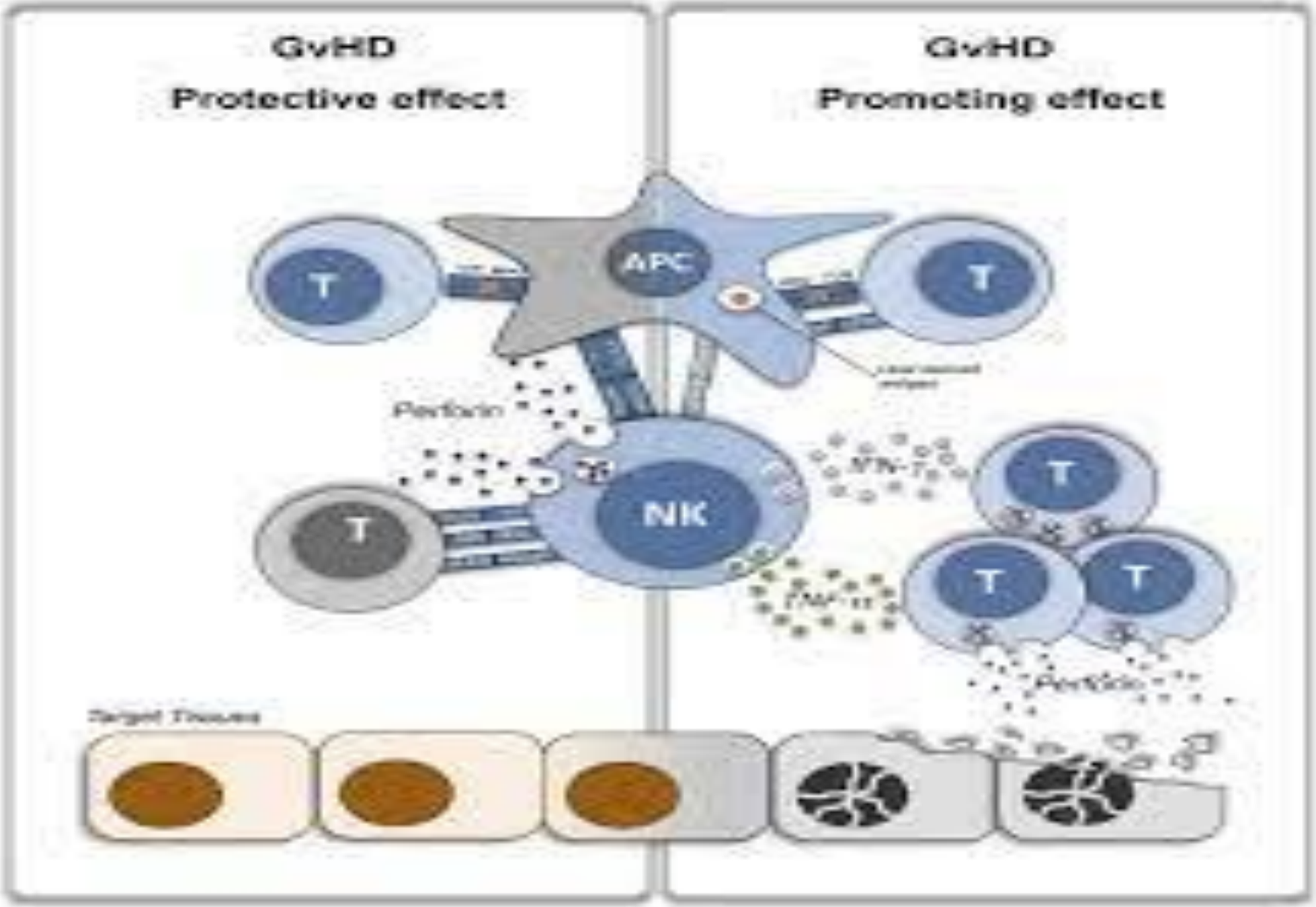
Patients	Disease	Graft-versus-Host Disease (GVHD) Prophylaxis	Acute/Chronic GVHD	TRM	EFS(DFS)/OS	Reference
28	HR-AML	FK506, MTX	39%/30%	10%	60%/67% (2 years)	[19]
37	PID	FK506, MTX; FK506, MMF; CYA, MTX	22%	3.3% (27% GF)	96.7% (15 months)	[20]
41	AL	MMF	10%/9%	N.A.	21/41 patients alive after 1.6 years	[21]
23	Non-malignant	None	13%/0%	9.3%	91% (2 years)	[16,22]
34	HR-AL	N.A.	5.9%/6.1%	14.7%	42%/54% (1 year)	[23]
80	AL	None	30%; no extensive chronic GVHD	5%	71%/72% (5 years)	[24]

Legend: HR-AML = high-risk acute myeloid leukaemia; CYA = cyclosporine-A; MTX = methotrexate; DFS = disease-free survival; EFS = event-free survival; OS = overall survival; GF = graft failure; PID = primary immune deficiencies; AL = acute leukaemia; HR-AL = high-risk acute leukaemia; MMF = mycophenolate mofetil; N.A. = not available; TRM = transplantation-related mortality.

Table 2. Clinical trials with CD45RA T-cell depletion.

Patients	Disease	Graft-Versus-Host Disease (GVHD) Prophylaxis	Acute/Chronic GVHD	TRM	EFS(DFS)/OS	Reference
35	High-risk leukaemia	Tacrolimus	66%; 9%	9%	70%/78% (2 years)	[29]
8	Solid tumours	Sirolimus	No acute GVHD or GF	1 patient died of sinusoidal obstruction syndrome	N.A. (median follow-up was 184 days)	[34]
17	Haematological malignancies	Sirolimus and MMF	17.6% grades III–IV acute GVHD/6 patients with signs of oral or skin chronic GVHD	11.7%	76.5% of patients alive at a median of 223 days after haematopoietic stem cell transplantation (HSCT)	[35]

DFS = disease-free survival; EFS = event-free survival; OS = overall survival; TRM = transplantation-related mortality; GF = graft failure; MMF = mycophenolate mofetil; N.A. = not available.


GvHD
Protective effect
GvHD
Promoting effect
APC
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Perforin
NK
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IFN-γ
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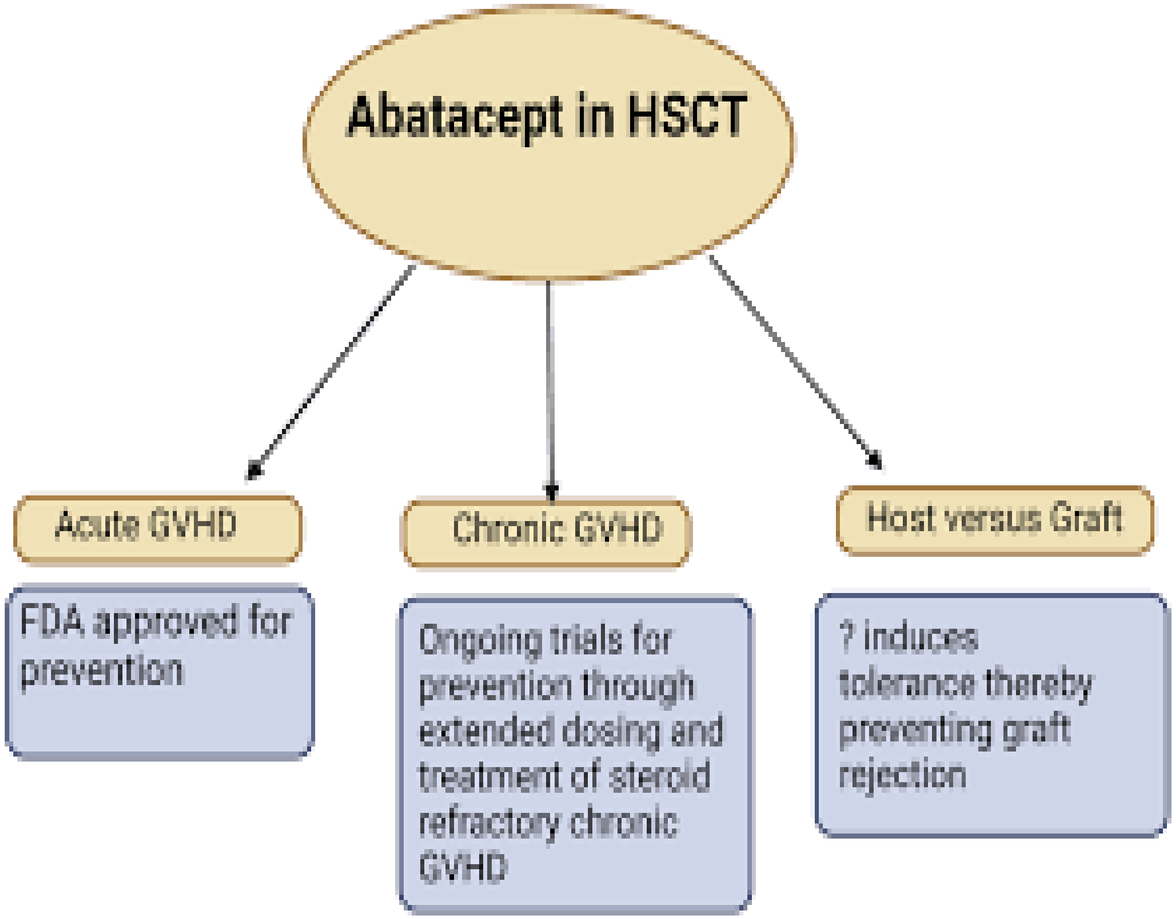
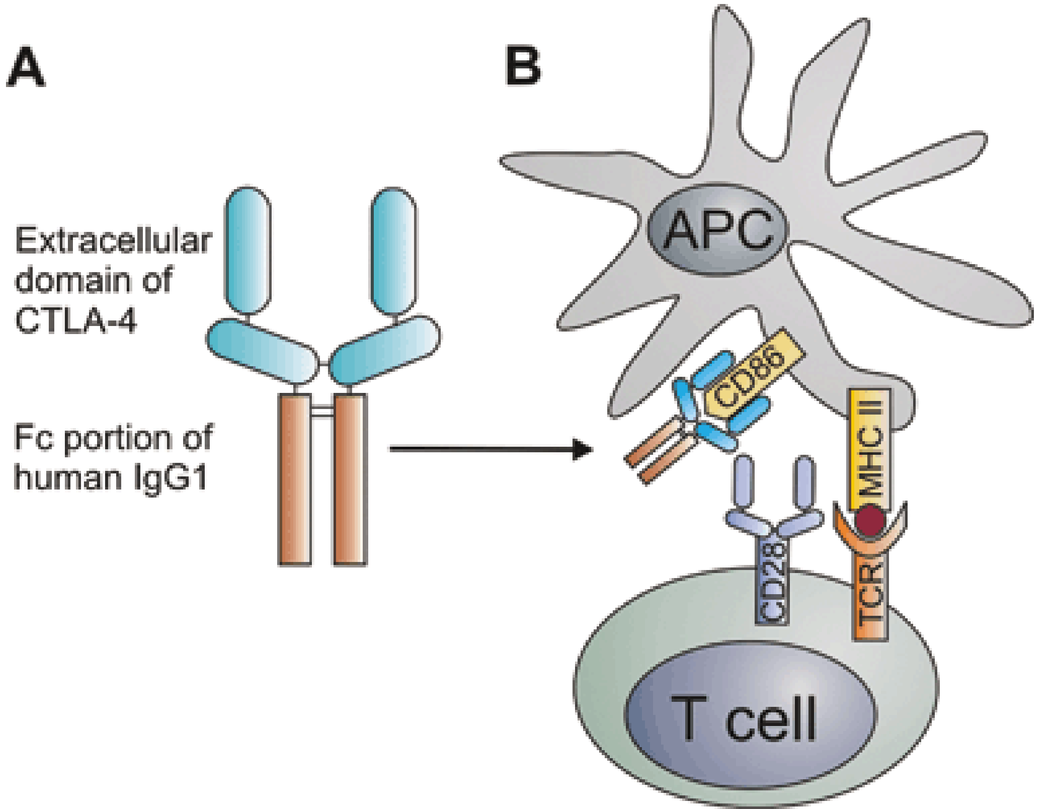
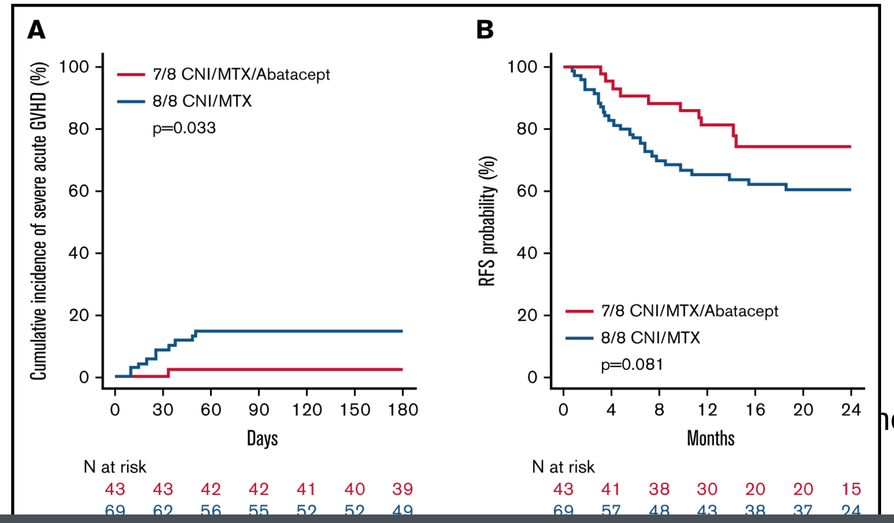
Target Tissues


Abatacept in HSCT
Acute GVHD
Chronic GVHD
Host versus Graft
FDA approved for prevention
Ongoing trials for prevention through extended dosing and treatment of steroid refractory chronic GVHD
? induces tolerance thereby preventing graft rejection


ORENCIA
(abatacept)


A
B
Extracellular domain of CTLA-4
Fc portion of human IgG1
APC
CD86
MHC II
CD28
TCR
T cell

Abatacept for GVHD prophylaxis can reduce racial disparities by abrogating the impact of mismatching in unrelated donor stem cell transplantation



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MANAGEMENT OF HIGH-RISK PATIENTS FOLLOWING ALLOGENEIC TRANSPLANT | JANUARY 5, 2023

How I prevent GVHD in high-risk patients: posttransplant cyclophosphamide and beyond

Joseph Rimando, Shannon R. McCurdy, Leo Luznik

Blood (2023) 141 (1): 49–59.

https://doi.org/10.1182/blood.2021015129

Article history

Table 1. Novel approaches to GVHD

Therapies	Mechanisms of action	Data	Ongoing clinical trials
Prevention			
Tocilizumab	Human monoclonal antibody against IL-6R	Phase 2 study of tocilizumab + Tac + MTX: 14% grade 2-4 acute GVHD, 3% grades 3 and 4 acute GVHD at 100 d[39]	NCT03434730
Abatacept	Costimulation blockade of CD28: CD80/86 to inhibit T cells	2 of 10 patients with grade 2-4 acute GVHD, no day 100 TRM[40]	NCT01743131 NCT02867800
Tregs	Regulate self-tolerance, limit GVHD while maintaining GVL effect	Modified expanded umbilical cord blood–derived Tregs: grade 2-4 acute GVHD 9% at 100 d[42]	NCT01660607 NCT00602693 NCT01818479 NCT01795573
T-cell depletion (CD34 selection and selective ex vivo T-cell depletion)	Depletion of alloreactive T cells and selective αβ T-cell depletion, with preservation of γδ T cells and NK cells	CD34+ selection: grade 2-4 acute GVHD 22.7%, chronic GVHD 6.8%[29]	NCT02323867 NCT02600208 NCT03301168 NCT03047746 NCT02345850
Statins	Inhibit proinflammatory Th-1 differentiation, induce Treg expansion, and downregulate APCs	Phase 2 study of statin to both donors and recipients with Tac + MTX—grade 2-4 3.3%; chronic GVHD 52.3%[46]	NCT03066466
Vorinostat	Histone deacetylase inhibitor decreases inflammatory cytokines, enhances Treg function, and reduces GVHD while preserving GVL	Phase 2 study of vorinostat + Tac + MTX: grade 2-4 acute GVHD 22%, grades 3 and 4 acute GVHD 8%; chronic GVHD 29%[51]	NCT01790568
JAK inhibitors (itacitinib, ruxolitinib)	Reduction of proinflammatory cytokines, T-cell activation and function, preserves Tregs, GVL effect	Preclinical studies and use in treatment setting	NCT03320642

Randomized Phase III BMT CTN Trial of Calcineurin Inhibitor–Free Chronic Graft-Versus-Host Disease Interventions in Myeloablative Hematopoietic Cell Transplantation for Hematologic Malignancies

Leo Luznik, MD[1]; Marcelo C. Pasquini, MD, MS[2]; Brent Logan, PhD[2]; Robert J. Soiffer, MD[3]; Juan Wu, PhD[4]; Steven M. Devine, MD[5]; Nancy Geller, PhD[6]; Sergio Giralt, MD[7]; Helen E. Heslop, MD[8]; Mary M. Horowitz, MD, MS[2]; Richard J. Jones, MD[1]; Mark R. Litzow, MD[9]; Adam Mendizabal, PhD[4]; Lori Muffly, MD[10]; Eneida R. Nemecek, MD[11]; Lynn O'Donnell, PhD[12]; Richard J. O'Reilly, MD[7]; Raquel Palencia, PharmD[13]; Johannes Schetelig, MD[13]; Leyla Shune, MD[14]; Scott R. Solomon, MD[15]; Sumithira Vasu, MD[12]; Vincent T. Ho, MD[3]; and Miguel-Angel Perales, MD[7]

abstract

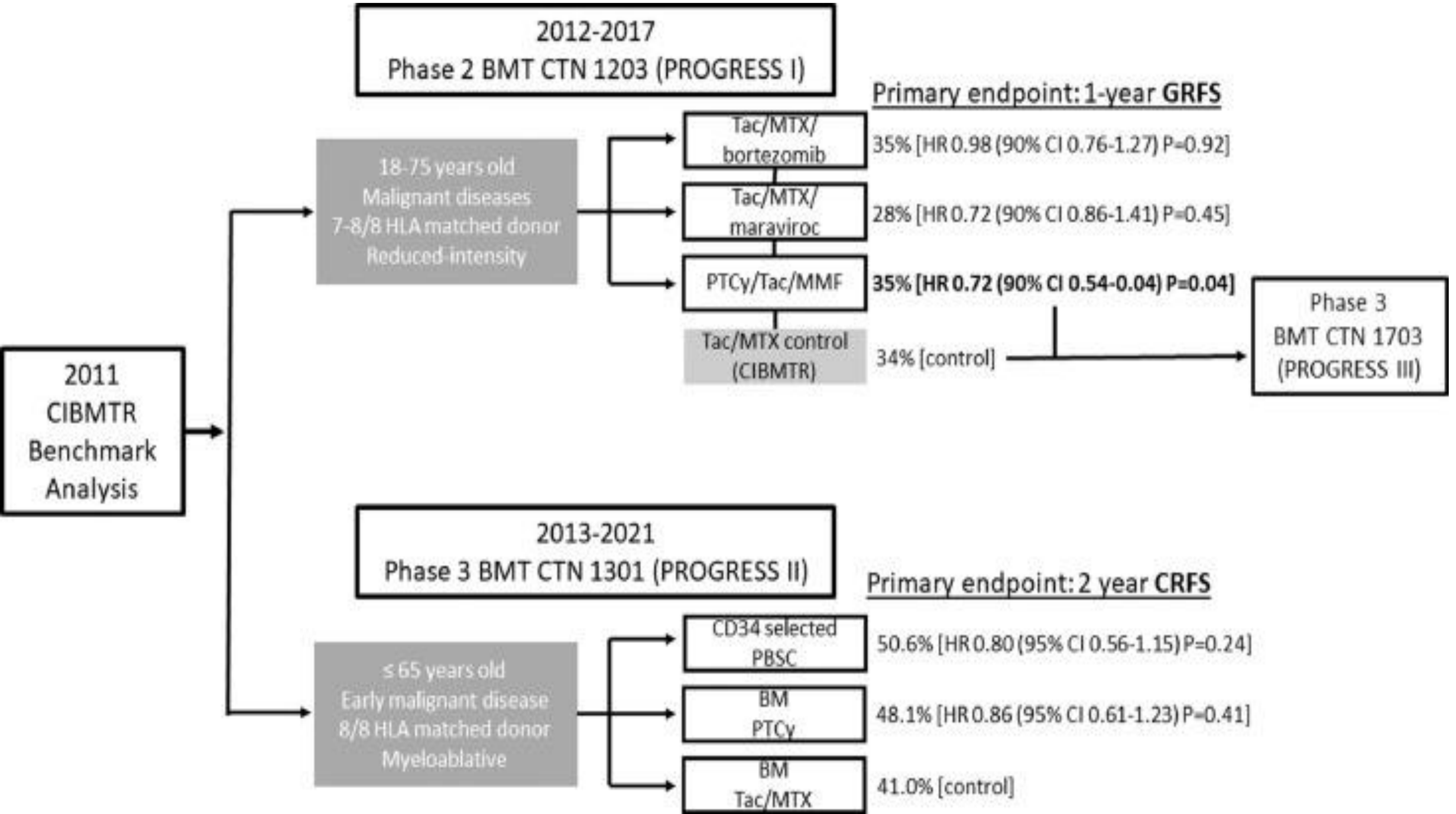
PURPOSE Calcineurin inhibitors (CNI) are standard components of graft-versus-host disease (GVHD) prophylaxis after hematopoietic cell transplantation (HCT). Prior data suggested that CNI-free approaches using donor T-cell depletion, either by ex vivo CD34 selection or in vivo post-transplant cyclophosphamide (PTCy) as a single agent, are associated with lower rates of chronic GVHD (cGVHD).

METHODS This multicenter phase III trial randomly assigned patients with acute leukemia or myelodysplasia and an HLA-matched donor to receive CD34-selected peripheral blood stem cell, PTCy after a bone marrow (BM) graft, or tacrolimus and methotrexate after BM graft (control). The primary end point was cGVHD (moderate or severe) or relapse-free survival (CRFS).

RESULTS Among 346 patients enrolled, 327 received HCT, 300 per protocol. Intent-to-treat rates of 2-year CRFS were 50.6% for CD34 selection (hazard ratio [HR] compared with control, 0.80; 95% CI, 0.56 to 1.15; $P = .24$), 48.1% for PTCy (HR, 0.86; 0.61 to 1.23; $P = .41$), and 41.0% for control. Corresponding rates of overall survival were 60.1% (HR, 1.74; 1.09 to 2.80; $P = .02$), 76.2% (HR, 1.02; 0.60 to 1.72; $P = .95$), and 76.1%. CD34 selection was associated with lower moderate to severe cGVHD (HR, 0.25; 0.12 to 0.52; $P = .02$) but higher transplant-related mortality (HR, 2.76; 1.26 to 6.06; $P = .01$). PTCy was associated with comparable cGVHD and survival outcomes to control, and a trend toward lower disease relapse (HR, 0.52; 0.28 to 0.96; $P = .037$).

CONCLUSION CNI-free interventions as performed herein did not result in superior CRFS compared with tacrolimus and methotrexate with BM. Lower rates of moderate and severe cGVHD did not translate into improved survival.

J Clin Oncol 40:356-368.


2012-2017
Phase 2 BMT CTN 1203 (PROGRESS I)
Primary endpoint: 1-year GRFS
18-75 years old
Malignant diseases
7-8/8 HLA matched donor
Reduced-intensity
Tac/MTX/ bortezomib
35% [HR 0.98 (90% CI 0.76-1.27) P=0.92]
Tac/MTX/ maraviroc
28% [HR 0.72 (90% CI 0.86-1.41) P=0.45]
PTCy/Tac/MMF
35% [HR 0.72 (90% CI 0.54-0.04) P=0.04]
Tac/MTX control (CIBMTR)
34% [control]
Phase 3
BMT CTN 1703
(PROGRESS III)
2011
CIBMTR
Benchmark
Analysis
2013-2021
Phase 3 BMT CTN 1301 (PROGRESS II)
Primary endpoint: 2 year CRFS
≤ 65 years old
Early malignant disease
8/8 HLA matched donor
Myeloablative
CD34 selected PBSC
50.6% [HR 0.80 (95% CI 0.56-1.15) P=0.24]
BM PTCy
48.1% [HR 0.86 (95% CI 0.61-1.23) P=0.41]
BM Tac/MTX
41.0% [control]

Details

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ARTICLE

The role of serum uric acid in the prediction of graft-versus-host disease in allogeneic hematopoietic stem cell transplantation

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Katayoon Ghasemi, Sayeh Parkhideh, Mohammad Hossein Kazemi, Maryam Salimi, Sina ... See all authors

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RESEARCH ARTICLE

WILEY

The role of serum uric acid in the prediction of graft-versus-host disease in allogeneic hematopoietic stem cell transplantation

Katayoon Ghasemi | Sayeh Parkhideh | Mohammad Hossein Kazemi | Maryam Salimi | Sina Salari | Ronak Nalini | Abbas Hajifathali

Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence
Abbas Hajifathali, Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran 1985711151, Iran.
Email: hajifathali@yahoo.com

Abstract

Background: Uric acid (UA) level is of the valuable signs of inflammation. However, the role of UA in the outcomes of hematopoietic stem cell transplantation (HSCT) such as GVHD and patients' overall survival is still a matter of debate. In this study, we aimed to evaluate the relationship between UA levels and GVHD incidence and overall survival in allogeneic HSCT patients.

Methods: A total of 201 patients who were admitted for allogeneic transplantation at Taleghani hospital, Tehran, Iran, were considered for retrospective analysis. Serum UA levels from 1 week before transplantation until 2 weeks after transplantation were used to determine thresholds and find out the association of serum UA levels with GVHD and overall survival.

Results: We showed that the determined thresholds using receiver operating characteristic curves have poor predictive value for GVHD and overall survival. The patients with serum UA higher than 3.4 mg/dL had 37% lower odds of GVHD incidence and 35% lower hazard of death than patients with UA lower than 3.4 mg/dL.

Conclusion: Our results indicated that serum UA levels lower than 3.4 mg/dL could significantly increase the incidence of GVHD and hazard of death. The antioxidant functions of UA could explain the lower incidence of GVHD in hyperuricemic patients. However, the inconsistencies of the previous studies require further investigation to elucidate the role of UA in the prediction of GVHD.

KEYWORDS
Allo-HSCT, GVHD prediction, uric acid

1 | INTRODUCTION

Today, the rate of allogeneic hematopoietic stem cell transplantations are performed annually, worldwide.[1] Graft-versus-host disease (GVHD) is a major complication and therapeutic challenge of allo-HSCT with the prevalence of 20%-60%.[2,3] During the

Int J Cancer Manag. 2022 April; 15(4):e120888. doi: 10.5812/ijcm-120888.

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Soluble T Cell Immunoglobulin and Mucin Domain-3 (sTIM-3) Predicts Graft-Versus-Host Disease (GVHD) in Iranian Allogeneic Hematopoietic Stem Cell Transplantation

Ronak Nalini [1, 2], Elham Roshandel [1], Maria Tavakoli Ardakani [3], Mohammad Hossein Kazemi [1], Haniyeh Ghaffari-Nazari [1], Abbas Hajifathali [1, *] and Masoud Soleimani [1, **]

[1] Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Department of Internal Medicine, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran
[3] Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[*] *Corresponding author*: Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: hajifathali@yahoo.com
[**] *Corresponding author*: Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: hema.197049@gmail.com

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Volume 60, Issue 2, April 2021, 103009

The apheresis content analysis in Allo-HSCT represents reliable influential factors on graft-versus-host disease and overall survival

Atefeh Rauofi, Abbas Hajifathali, Samira Karami, Farzaneh Tavakoli, Elham Roshandel, Hossein Bonakchi, Sayeh Parkhideh

Show more

Material and methods

We analyzed 87 patients with hematological malignancies who underwent allogeneic hematopoietic stem cell transplantation at the Taleghani Stem Cell Transplantation and Cell therapy center, Tehran, Iran from January 2016 to December 2018. Patients were conditioned with either myeloablative conditioning regimen or reduced-intensity regimen.

Result

A $CD34^+$ cell dose < 4.35×10^6/kg and $CD3^+$ cell dose < 365×10^6/kg was associated with higher survival and lower acute and chronic GVHD incidence, although their association was not statistically significant. Moreover, there was a significant association between MNC count < 6.15×10^8/kg and acute GVHD incidence.

مرکز آموزش و پژوهش در بیماری های پوست و جذام

پروپوزال طرح پژوهشی

با عنوان:

بررسی ریسک فاکتور های GVHD مزمن پوستی به دنبال انجام پیوند سلول های بنیادی خون ساز غیر همنوع در جمعیت بیماران ایرانی

استاد راهنما :

دکتر علیرضا فیروز

اساتید مشاور :

دکتر مهشید مهدیزاده

دکتر مریم دانش پژوه

نگارش: دکتر شایان زمانی

عنوان طرح تحقیقاتی : بررسی اثربخشی داروی Baricitinib در درمان GVHD مزمن به همراه درگیری پوستی در بیماران پیوند مغز استخوان آلوژنیک

Title : Evauation of Baricitinib as a possible treatment for chronic GVHD with cutaneous involvement among allogeic HCT patients

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تاریخ این ویراست:

مشخصات کلی و چکیده طرح

عنوان فارسی طرح

بررسی اثربخشی داروی Baricitinib در درمان GVHD مزمن به همراه درگیری پوستی در بیماران پیوند مغز استخوان آلوژنیک

عنوان انگلیسی طرح

Evauation of Baricitinib as a possible treatment for chronic GVHD with cutaneous involvement among allogeic HCT patients

Patient No.	Diagnosis	Age	Donor	Type of Graft manipulation	Gvhd
1 (SF)	SAA	34	Unrelated (9/10)	CD34 Selection	NO
2 (ST)	AML	38	Related (FM)	CD3/CD19 depletion	NO
3 (KR)	SAA	29	Related (FM)	CD34 Selection	NO
4 (NF)	SAA	30	Related (FM)	CD34 Selection	NO
5 (RR)	MD	7	Haplo-father	CD3/CD19 depletion	NO
6 (ANA)	SAA	29	Related (FM)	CD34 Selection	NO
7 (MA)	SAA	26	Unrelated (9/10)	CD34 Selection	NO
8 (ZG)	AML	27	Unrelated (FM)	CD3/CD19 depletion+T cell Add-back	NO
9 (HR)	HD	17	Haplo-brother	CD3/CD19 depletion+T cell Add-back	Grade I
10 (MJ)	NHL	37	Related (FM)	CD34 selection +T cell Add-back	NO
11 (FY)	AML	19	Haplo-Sister	CD34 Selection + T cell Add-back	NO
12 (AZ)	AML	16	Haplo-mother	CD34 Selection + T cell Add-back	NO
13 (FF)	AA	22	Haplo-sister	CD3/CD19 depletion	NO
14 (EA)	AML	18	Unrelated (9/10)	CD3 Selection	NO
15 (HF)	ALL	42	Related (FM)	CD3/CD19 depletion	Grade III
16 (MM)	AML	52	Haplo-brother	CD3/CD19 depletion	HC
17 (AS)	SAA	40	Haplo-sister	CD3/CD19 depletion	Grade IV
18 (MF)	SAA	35	Unrelateed (FM)	CD3 Selection	NO
19 (MA)	AML	55	Related (9/10)	CD3/CD19 depletion	Grade II
20 (SF)	MD	7	Related (FM)	TCRα$^{\beta}$/CD19 Depletion	NO

Take home

- Choose an appropriate combination of immunosuppressants with respect to the pharmacokinetics and pharmacodynamics in the target species

- Single-drug protocols should be limited to verified exemptions

- Along with the changing transplant population, the field of HCT has dramatically shifted in the past decade because of the widespread adoption of posttransplantation cyclophosphamide (PTCy), which has increased the use of HLA-mismatched related donors to levels comparable to HLA-matched related donors.

- Role of biomarkers
- Preventive algorithm based on biology
- Graft manipulation accessible for bmt ward


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Case Presentation 1 : An adolescent (21 year old) male patient with acute lymphoblastic leukemia (ALL) Primary Induction Treatment Failure (Inotuzumab Ozogamicin)/Post HSCT

- Myeloid and Platelet Engraftment occurred on day +12 and +15 respectively

- Day 11 methotrexate was 50% dose reduced, and leucovorin rescue was added for severe mucositis

- **On day +18 post transplant :** he developed a patchy maculopapular skin rash involving a body surface area (BSA) of <20% Erythematous maculopapular rash; both palmars

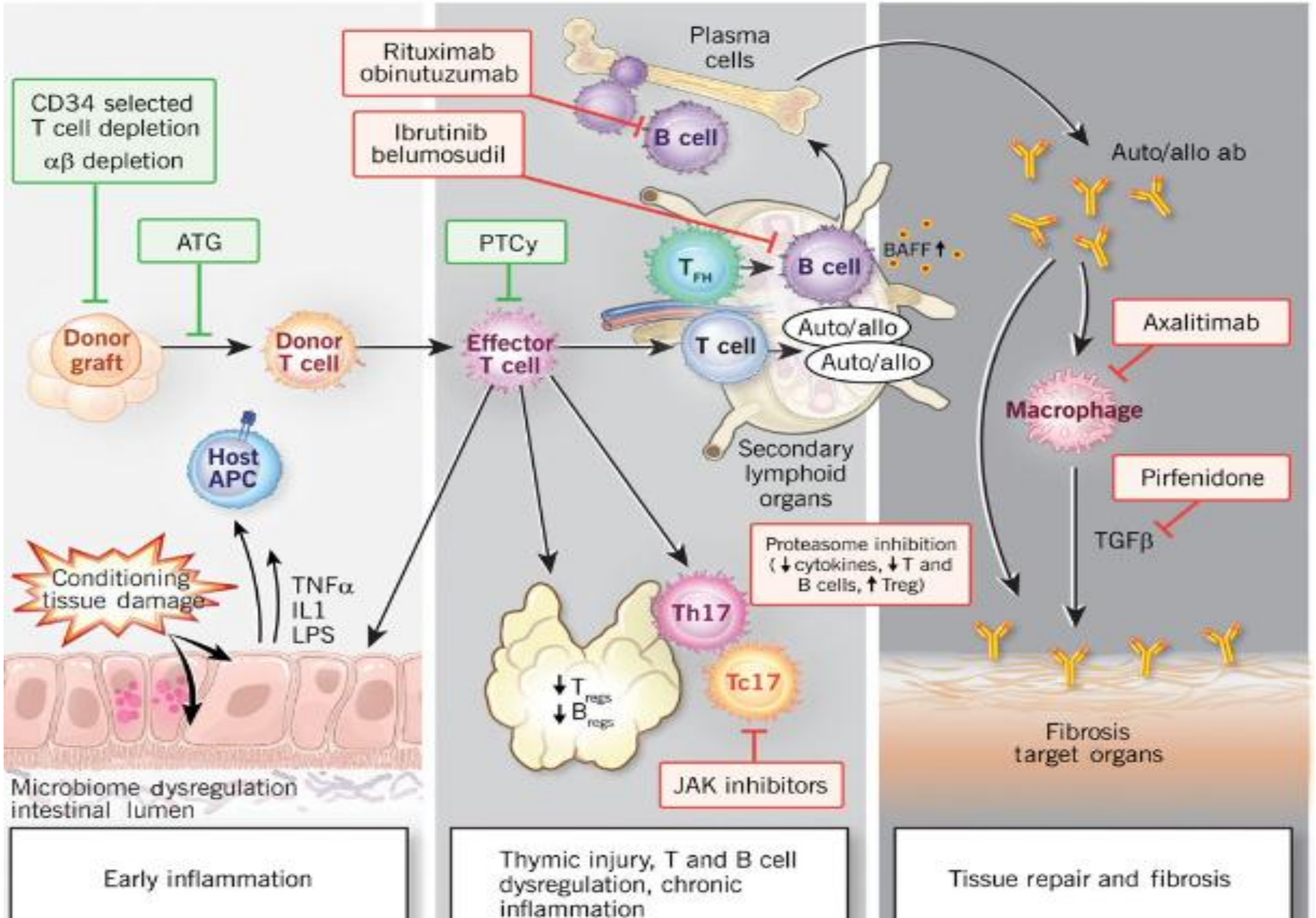
Topical steroid started and was started on 0.1% triamcinolone topical cream.

- **On day +20 post transplant:**

Worsening Erythematous maculopapular rash involving his face, anterior/posterior torso, and lower extremities to his knees (60% BSA). He had stage 3 skin, more than 60% BSA (acute skin GvHD stage III)

Watery diarrhea; six times/day (1200 cc) (acute lower GI GvHD stage II)

Acute GvHD Grade III (MAGIC Criteria for GvHD grading)


CD34 selected T cell depletion
αβ depletion
ATG
Donor graft
Donor T cell
Host APC
Conditioning tissue damage
TNFα
IL1
LPS
Microbiome dysregulation intestinal lumen
Rituximab obinutuzumab
Ibrutinib belumosudil
Plasma cells
B cell
PTCy
Effector T cell
T cell
Auto/allo
Auto/allo
T$_{FH}$
B cell
BAFF↑
Secondary lymphoid organs
Auto/allo ab
Axalitimab
Macrophage
Pirfenidone
TGFβ
Proteasome inhibition (↓cytokines, ↓T and B cells, ↑Treg)
Th17
Tc17
↓T$_{regs}$
↓B$_{regs}$
JAK inhibitors
Fibrosis target organs
Early inflammation
Thymic injury, T and B cell dysregulation, chronic inflammation
Tissue repair and fibrosis

Case Presentation 1 : An adolescent (21 year old) male patient with acute lymphoblastic leukemia (ALL) Post-HSCT/ Acute GvHD

- Methylprednisolon 2mg/kg & Cyclosporine in therapeutic level

- On day +5 after recieving Methylprednisolon (+26 post transplant):
  Skin GvHD stage II
  Watery and bloody diarrhea, 7 times/day (1600 cc)

DDX: GI GvHD or CMV Colitis?

Indication of Biopsy in aGVHD

what’s Therapeutic decision?

Dr. Dabiri

TCT | TRANSPLANTATION & CELLULAR THERAPY MEETINGS℠ of ASBMT™ AND CIBMTR®

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

How I Treat: Steroid Refractory Acute Graft-versus-Host Disease

Amin M. Alousi, MD
Professor of Medicine
Director, GVHD Multidiscipline Clinic and Research Program
Department of Stem Cell Transplantation and Cellular Therapy

~~GVHD~~

STEROID REFRACTORY ACUTE GRAFT-VERSUS-HOST DISEASE (SR-acute GVHD)

- SR-acute GVHD Population:
  - Generally Defined as:

    No Response or progression on steroids OR flare in aGVHD while on high-doses of steroids (>0.5-1mg per kg)
  - Difficult group to study (or positively impact)
  - Even when GVHD responds; NRM remains high from infection and organ toxicity

NRM-non-relapse mortality

TRENDS IN ACUTE GVHD: A COMPARISON OF 1999 THROUGH 2012

	1999-2001 (n=497)	Year of transplant 2002-2005 (n=962)	2006-2012 (n=1446	P-Value
Age, median (range), years	34 (1 - 63)	37 (<1 - 67)	43 (<1 - 70)	<0.001
Male sex, n (%)	284 (57)	583 (61)	805 (56)	0.06
Race Caucasian, n (%)	429 (86)	799 (83)	1174 (81)	0.05
Karnofsky score > 90% at transplant, n (%)	320 (64)	609 (63)	915 (63)	<0.001
Diagnosis, n (%)				<0.001
Acute myeloid leukemia	257 (52)	502 (52)	879 (61)	
Acute lymphoblastic leukemia	167 (34)	343 (36)	364 (25)	
Myelodysplastic syndromes	73 (15)	117 (12)	203 (14)	
Disease status at transplant*, n (%)				<0.001
Early	166 (33)	417 (43)	766 (53)	
Intermediate	158 (32)	272 (28)	298 (21)	
Advanced	173 (35)	267 (28)	370 (26)	
Unknown	0	6 (<1)	12 (<1)	
HLA-identical sibling donor age, years, median (range)	40 (<1 - 67)	43 (1 - 71)	47 (2 - 75)	0.001
Unrelated donor age, years, median (range)	35 (19 - 59)	35 (18 - 59)	33 (18 - 61)	<0.001
Donor/recipient sex match, n (%)				0.50
Female/male	103 (21)	209 (22)	285 (20)	
Other	395 (79)	753 (78)	1160 (80)	
Donor/recipient CMV status, n (%)				<0.001
+/+	91 (18)	232 (24)	386 (27)	
+/-	61 (12)	99 (10)	177 (12)	
-/+	129 (26)	310 (32)	435 (30)	
-/-	194 (39)	296 (31)	415 (29)	
Missing	22 (4)	25 (3)	33 (2)	
Donor/recipient HLA match**, n (%)				<0.001
HLA-identical sibling	107 (22)	166 (17)	424 (29)	
URD well-matched	171 (34)	497 (52)	764 (53)	
URD partially matched	149 (30)	221 (23)	207 (14)	
URD mismatched	70 (14)	77 (8)	25 (2)	
URD missing	0	1 (<1)	26 (2)	
Time from diagnosis to transplant, months, median (range)	9 (<1 - 238)	7 (<1 - 197)	6 (<1 - 279)	<0.001
TBI-based conditioning regimen, n (%)	371 (75)	640 (67)	748 (52)	<0.001
Marrow graft, n (%)	313 (63)	346 (36)	329 (23)	<0.001
Blood graft, n (%)	184 (			
GvHD prophylaxis, n (%)				
Cyclosporine-based	359 (			
Tacrolimus-based	132 (			
Acute GvHD grade				
II	219 (			
III	190 (			
IV	88 (			
Acute GvHD-effected organs				
Skin + Gut + Liver	133 (			
Skin + Gut	125 (			
Skin + Liver	70 (			
Gut + Liver	21 (			
Skin only	85 (			
Gut only	56 (			
Liver only	7 (			
Acute GvHD treatment, n (%)				
Steroids + ATG + others	47 (			
Steroids + MAB + others	51 (			
Steroids only	389 (			
Missing	19 (			
Time from transplant to acute GvHD grade II-IV onset, days, median (range)	23 (			
< 2 weeks, n (%)	123 (			
2-4 weeks, n (%)	221 (			
1-2 months, n (%)	128 (			
2 months – 100 days, n (%)	25 (			
Follow-up of survivors, months, median (range)	144 (			

CMV: cytomegalovirus; HLA: human leukocyte antigen; URD: unrelated; TBI: total
categorized as follows: Early: acute myeloid leukemia/acute lymphoblastic leu
mia with ringed sideroblasts/pre-HCT marrow blasts <5%); Intermediate: acute myeloid leukemia/acute lymphoblastic leukemia (second complete remission or beyond);
Advanced: acute myeloid leukemia/acute lymphoblastic leukemia (relapse/primary induction failure) myelodysplastic syndromes (refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, chronic myelomonocytic leukemia or marrow blasts ≥5%). **Donor-recipient matching definitions as previously defined by Weisdorf, *et al.* 2008.*

2006-2012
N=1446

2002-2005
N=972

1999-2001
N=497

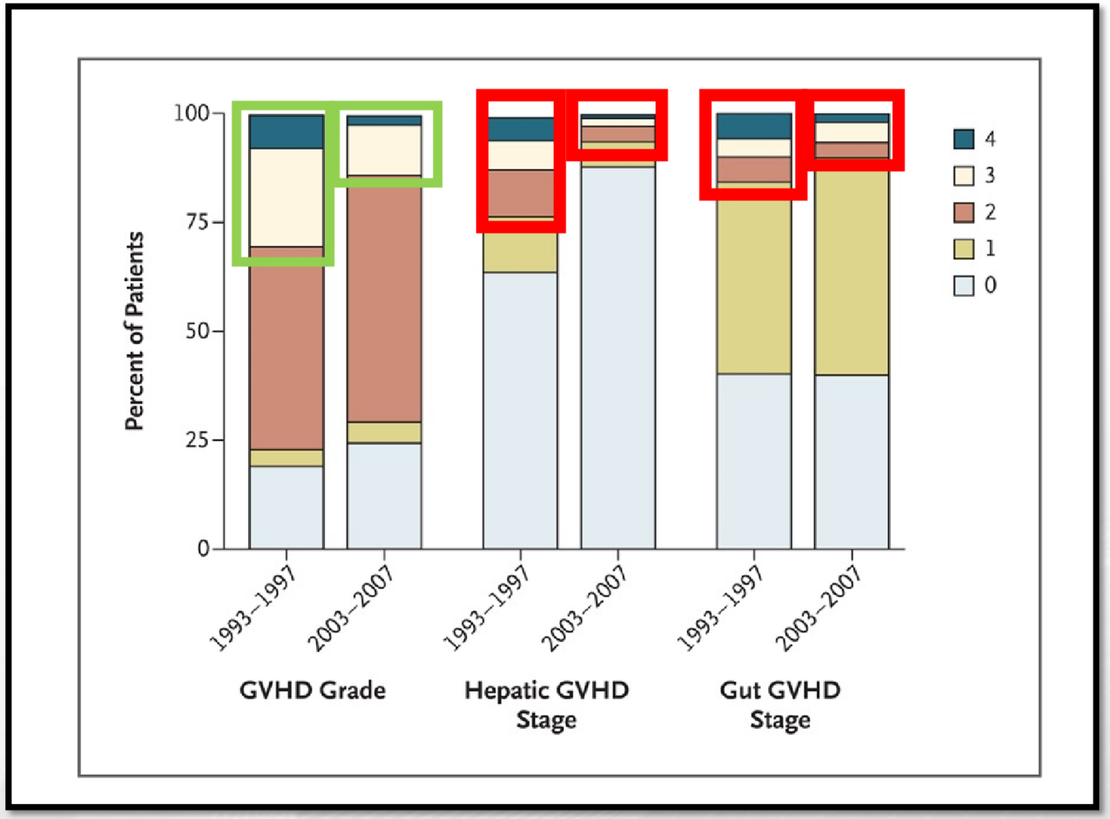
		1999-2001	2002-2005	2006-2012	
Acute GvHD grade					<0.001
II	II	219 (44) 44%	507 (53) 53%	904 (63) 63%	
III		190 (38)	310 (32)	368 (25)	
IV	III/IV	88 (18) 56%	145 (15) 47%	174 (12) 37%	
Acute GvHD-effected organs					<0.001
Skin + Gut + Liver		133 (27)	189 (20)	193 (13)	
Skin + Gut		125 (25)	289 (30)	562 (39)	
Skin + Liver		70 (14)	72 (7)	63 (4)	
Gut + Liver		21 (4)	42 (4)	42 (3)	
Skin only		85 (17)	201 (21)	224 (15)	
Gut only		56 (11)	153 (16)	345 (24)	
Liver only		7 (1)	16 (2)	17 (1)	

> II and < III/IV in Modern Era

Less Multi-organ in Modern Era

Khoury HJ, et al. Haematologica 2017;102:958-966

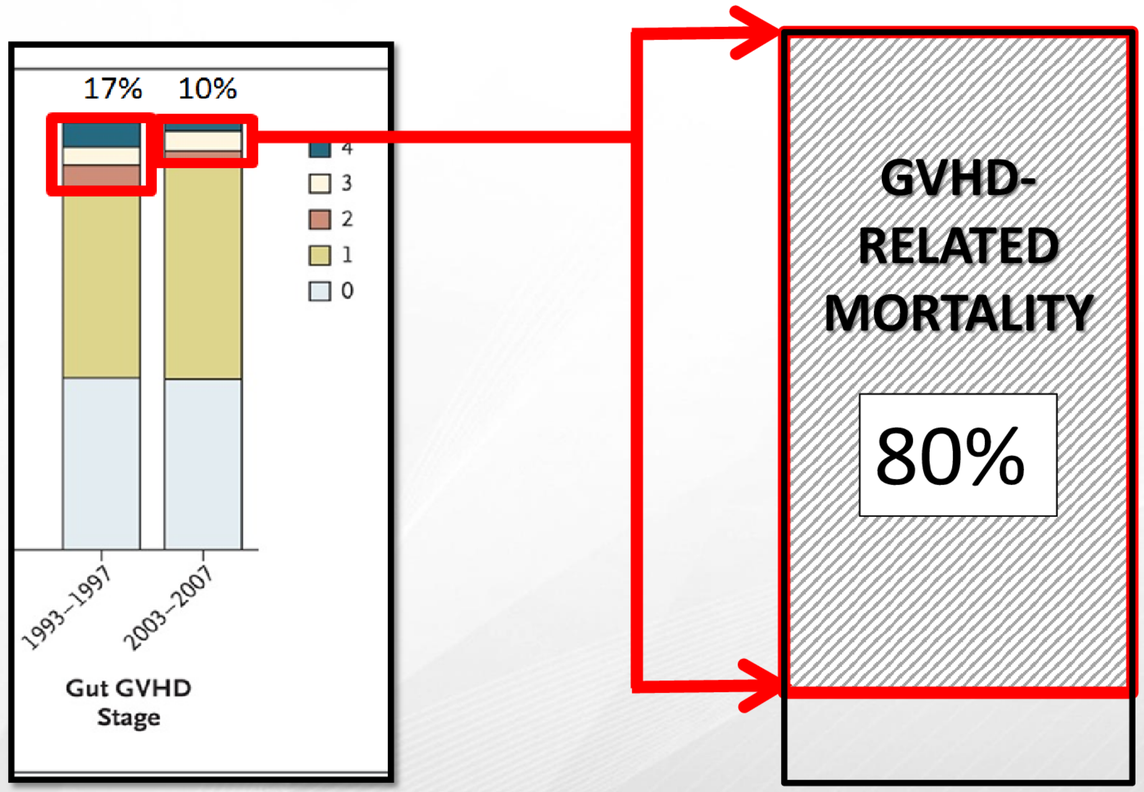
TRENDS IN ACUTE GVHD:
REDUCTION IN OVERALL GRADE 3-4, LIVER AND SEVERE GI



Golley T, et al. N Engl J Med 2010;363:2091-101

GI-gastrointestinal

Steroid-Refractory Lower GI GVHD Contributes to Majority of GVHD-related mortality



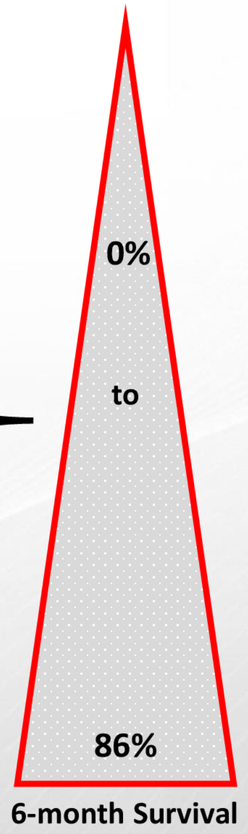
Golley T, et al. N Engl J Med 2010;363:2091-101

SR-acute GVHD

- Definition
  - *Progression of organ stage after 3 days of high dose steroids (2mg/kg/day)*
  - *No response to high dose steroids (2mg/kg/day) by day 7-10*
  - *Flare after initial response following taper of steroids below specified dose (for instance 0.5mg- 1mg/kg/day) (often referred to steroid-dependent)*

Summary of Studies Evaluating Agents for Second-line therapy for acute GVHD: Reported 6-month Survival

Agent	Phase	No. of patients	Response Assessment	CR Proportion	CR or PR Proportion	6-month Survival
Methotrexate	Retro	12	Day 28[1]	0.42	0.58	0.58
MMF	Retro	13	Best	0.15	0.46	0.66
MMF	Retro	10	Best	0	0.60	0.77
MMF	Retro	48	Best	0.31	**0.79**	0.47
MMF	Retro	27	Best	0.26		0.52
ECP	Retro	33	Best[2]	**0.55**	0.76	**0.76**
ECP	Retro	23	Best[2]	0.48	0.48	0.57
Basiliximab	2	23	Day 7[1]	0.17	0.83	0.55
Daclizumab	2	43	Day 43	0.37	0.51	
Daclizumab	2	12	Day 28[1]	0.08	0.50	0.33
Daclizumab	Retro	57	Day 43	0.33	0.54	**0.28**
Inolimomab	2	14	Best[2]	0.14	0.43	0.36
Denileukin diftitox	1	32	Best	0.38	0.53	
Denileukin diftitox	2	22	Best	0.18	**0.27**	
Alemtuzumab	2	18	Day 28[1]	0.33	0.83	0.71
Alemtuzumab	2	10	Best[2]	0.20	0.50	**0**
Alemtuzumab	Retro	18	Day 56[1]	0.28	0.62	0.61
Horse ATG	Retro	22	Day 28		**0.18**	
Horse ATG	Retro	58	Day 21[1]	**0.07**	**0.28**	**0.17**
Horse ATG	Retro	79	Day 28	0.20	0.54	0.44
Horse ATG	2/3	47	Best[2]	0.32	0.57	0.45
Horse ATG	3	27	Best[2]	0.33	0.56	0.55
Etanercept	Retro	13	Day 56	0.38	0.46	0.77
Infliximab	Retro	21	Day 7[1]	**0.62**	0.67	0.52
Horse ATG + Etanercept	Retro	16	Best[2]	**0.69**	0.81	0.56
Daclizt+Etanercept	2	21	Best[2]	0.38	0.67	0.57
Daclizt+Infliximab	Retro	22	Day 42[1]	0.45	0.82	**0.86**
Daclizt/Inflix/Horse ATG	Retro	12	Best[2]	**1.00**	**1.00**	0.73
Sirolimus	Retro	34	Best	0.44	0.76	0.48



Martin PJ, et al. Biol Blood Marrow Transplant 2012;18:1150-1163

Factors Predictive of Outcome in SR-aGVHD Trials

- Patient Age
- Acute GVHD Type (skin vs. visceral; single vs. multiple organs)
- Time from acute GVHD onset/steroids to second-line agent

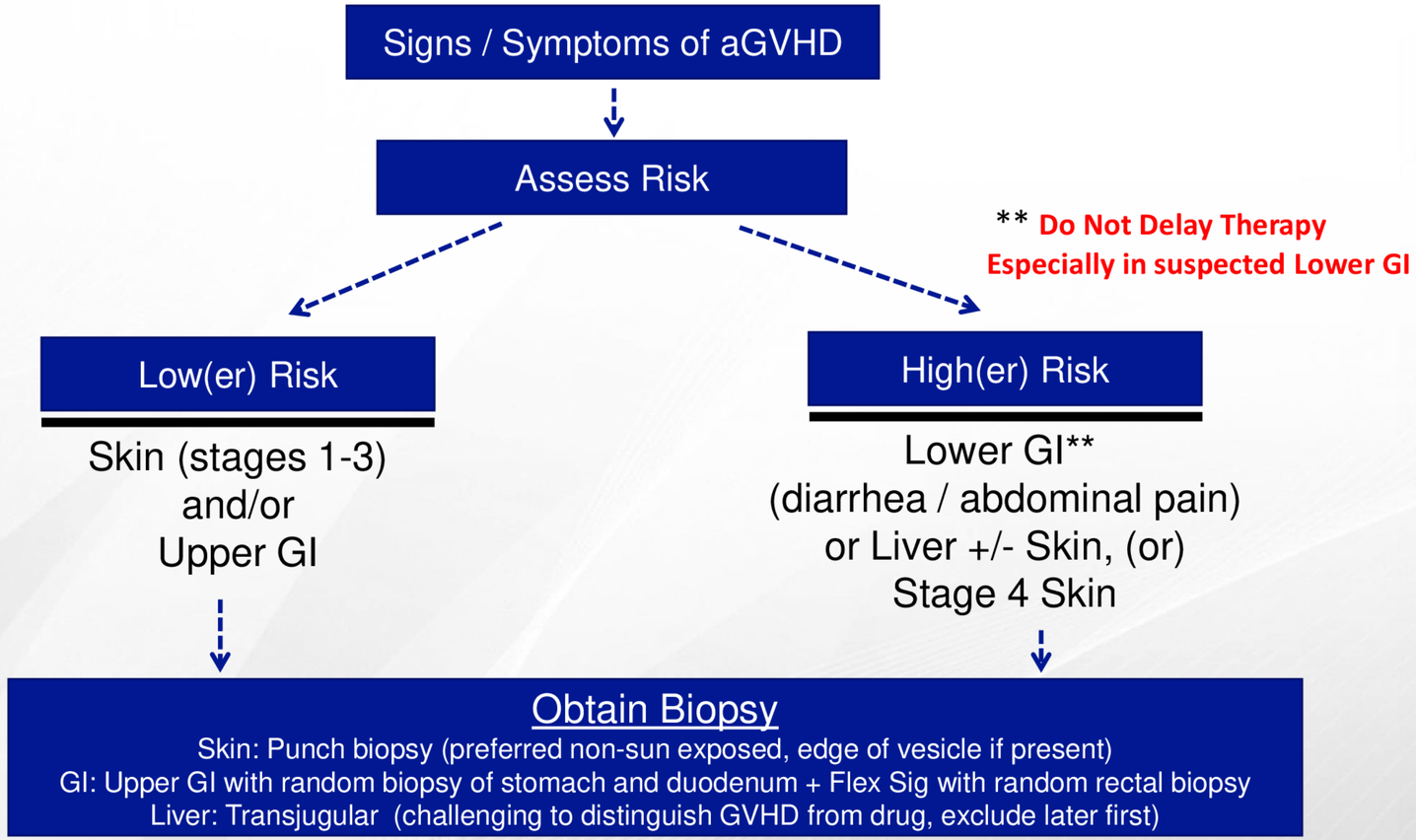
Conclusion: Biomarkers on Day 7 of Steroids

- Independently is correlated with **response** at 4 weeks, **NRM** and **OS**.
- In patients who have not achieved a response by day 7 (progressed or NR) Biomarkers (ST2 and Reg3α):
  - Identify a Low and High Risk Population
  - Low Risk Population = "*slow responders*"
  - Low Risk Population have long-term outcomes including NRM similar to those who respond by day 7
  - Roughly 50% of patients are in this category

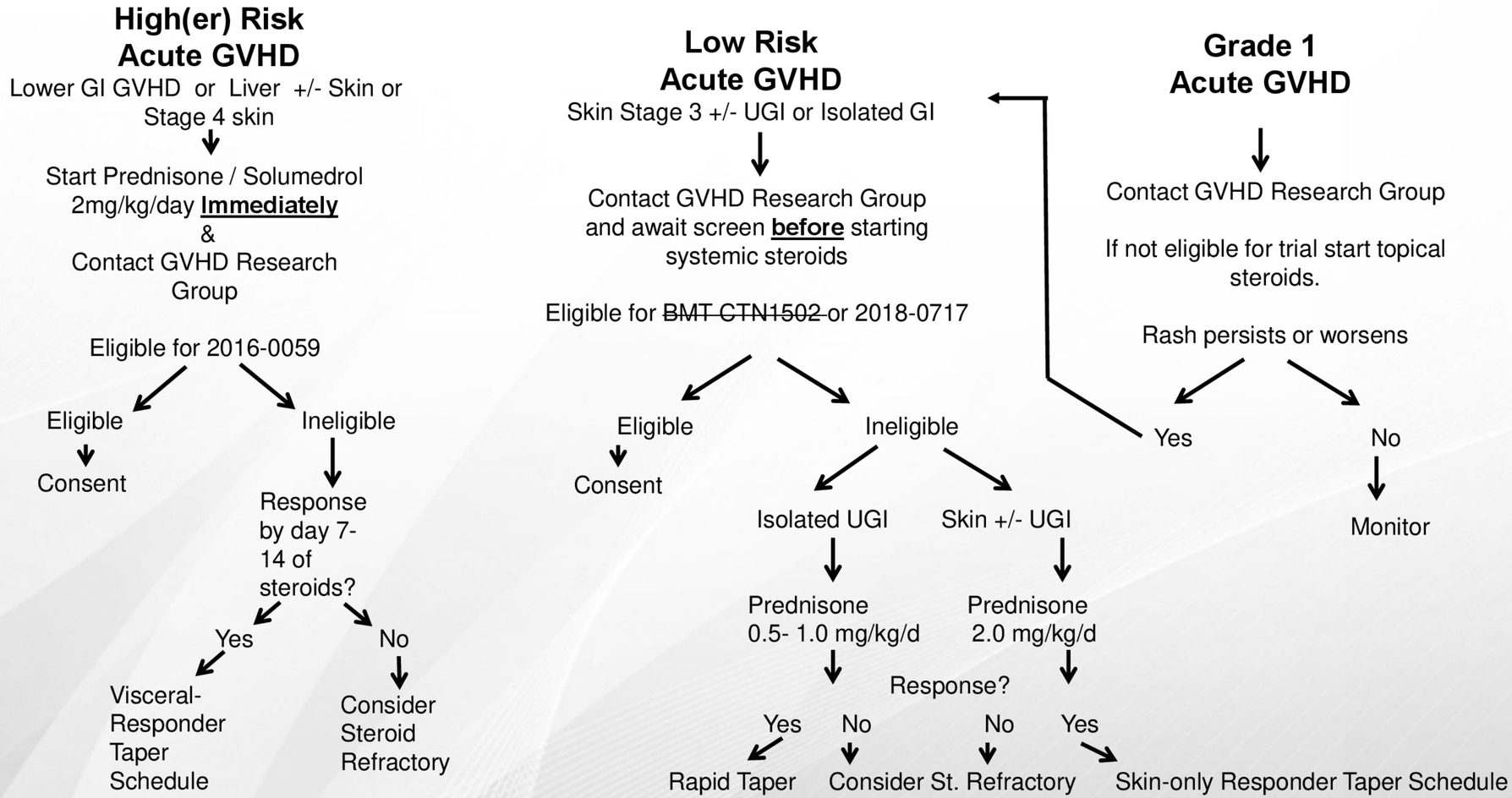
Major-Monfried H, et al. Blood 2018;131:2846-2855

OS-Overall Survival; NR-nonresponder;
ST2-suppressor of tumorigenicity-2;
Reg3α-regenerating islet-derived protein 3-α

MD Anderson: aGVHD Algorithm



MD Anderson: acute GVHD Treatment Algorithm



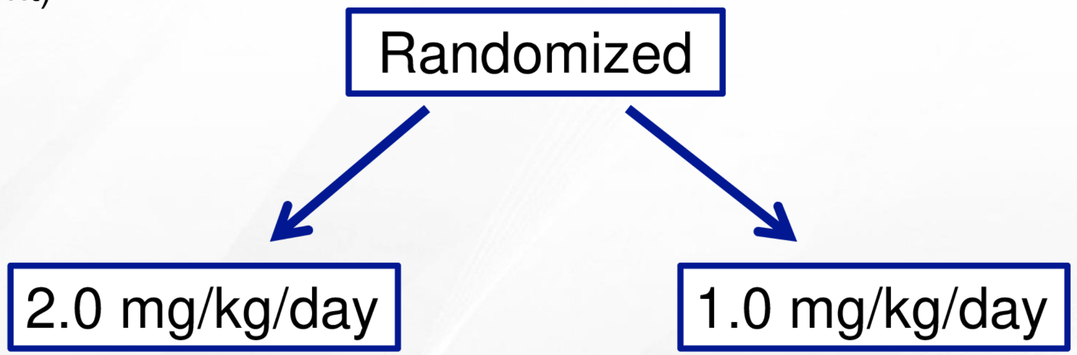
ACUTE GI GVHD

- **Assessment**
  - History and Physical
  - Consider Admission to Expedite Work-up and Treatment
  - Strict I/O
  - Measurement and evaluation of stool
- **Diagnosis**
  - GI Consult
  - Upper endoscopy and/or flex sigmoidoscopy / colonoscopy
  - **DO NOT** wait for completion of these procedures to start systemic therapy
  - Stool culture for: *Clostridium difficile*
- **Interventions**
  - Diet as tolerated
  - Dietary consult: Diet As Tolerated *(Lack of Evidence for GVHD Graduated Diet)*
  - Perianal skin care: Sitz baths and NDX cream (nystatin, zinc oxide, lidocaine)
  - Physical Therapy consult
  - Endocrine consult
- For lower GI GVHD +/- upper GI GVHD: SYSTEMIC THERAPY – Clinical Trial
  - ****Contact GVHD attending or research nurse****
  - **First-line therapy:** Prednisone 2 mg/kg/day PO as two divided doses or methylprednisolone equivalent IV/PO (based on IBW).
    - Continue tacrolimus IV or PO as clinically appropriate
  - **Suggested Second-line therapy**:
    Ruxolitinib, Pentostatin, ECP, Siro + Low Dose Tac, Entanercept, Vedolizumab
  - **Supportive care options to consider:**
    - Loperamide +/- dipenoxylate/atropine
    - Octreotide 250 to 500 mcg IV q 8 hrs if diarrhea volume > 500 ml after 24 hours of loperamide and/or diphenoxylate/atropine or tincture of opium
    - Stop octreotide as soon as diarrhea has resolved, but re-assess every 4 to 7 days
    - If no response at 4 to 7 days continuing octreotide is **NOT** recommended
    - Budesonide 3 mg PO TID

I/O-input and output; ECP-photopheresis; Siro-Sirolimus; Tac-Tacrolimus

Initial Dose of Steroids for acute GVHD

- Prospective randomized study of high versus low dose steroids:
  - Grade IIb to IV acute GVHD (Rash ≥ 50% BSA, Stool Volume > 1 liter and any liver involvement)

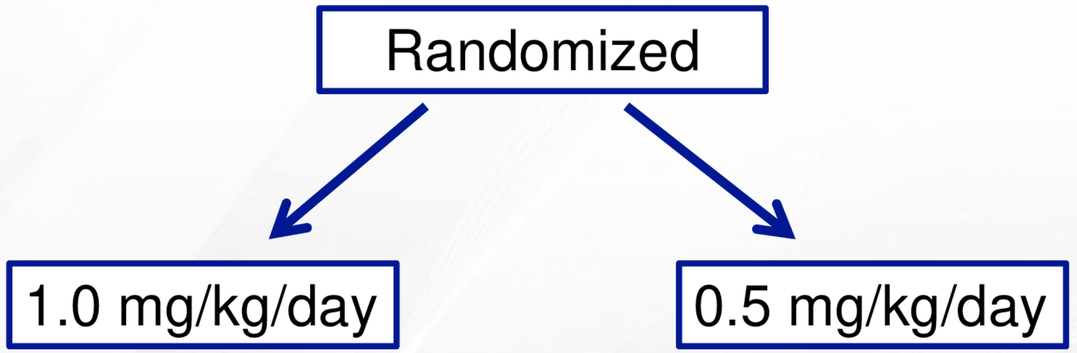


Mielcarek M, et al. Haematologica 2015;10:842-848.

BSA-body surface area

Initial Dose of Steroids for aGVHD

- Prospective randomized study of high versus low dose steroids:
  - Grade IIa acute GVHD (**Upper GI GVHD**, Stool Volume < 1 liter, rash <50% and no liver involvement)



Prednisone-equivalent dosing

Mielcarek M, et al. Haematologica 2015;10:842-848.

No Impact on Reduction in Cumulative Dose

- Primary Outcome: 33% reduction in Day 42 Cumulative Dose of Steroids
- Grade IIa Cohort: 1mg/kg vs. 0.5mg/kg/day Initial Dose
  - 27mg/kg vs. 22 mg/kg (18% reduction, p=0.08)
- Grade IIb-IV Cohort: 2mg/kg vs. 1mg/kg/day Initial Dose
  - 41mg/kg vs. 38mg/kg (7% reduction, p=0.4)

Mielcarek M, et al. Haematologica 2015;10:842-848.

Secondary Measures of Benefit or Detriment to Lower Dose

- Secondary Outcomes
  - Measures of prednisone toxicity (infections, hyperglycemia)
  - Possible harm (progression to Grade III/IV GVHD, secondary therapy for refractory GVHD, non-relapse mortality, recurrent malignancy).

- Grade IIb-IV Cohort:
  - No difference in NRM, Relapse and OS.
  - Need for second-line: Lower-dose prednisone resulted in higher need for secondary therapy than 2mg/kg/day **(41% vs 7%, p=0.001).**
  - Trend suggested an increase in the risk of progression to Grade III-IV acute GVHD (19% vs 7%, p=0.2).
  - The risks of infection and measures of glycemic control were not affected by initially assigned prednisone dose.

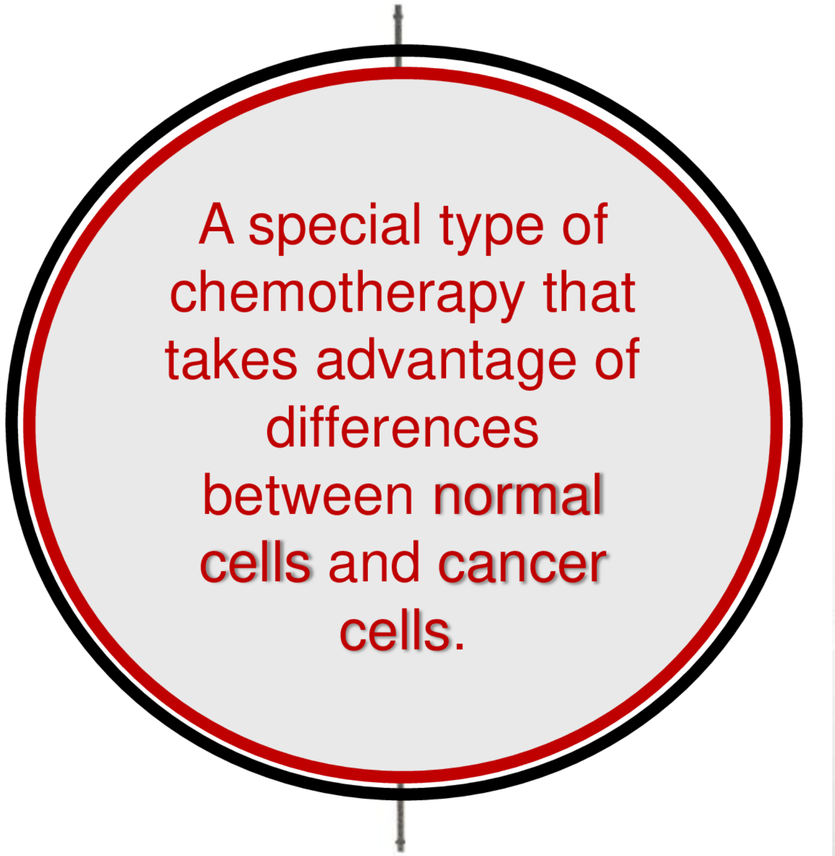
Mielcarek M, et al. Haematologica 2015;10:842-848.

Conclusions: My Take on the Paper

- Acute GVHD Limited to Upper GI GVHD and Skin Rash <50%.
  - —Patients started on 0.5mg/kg/day vs. 1mg/kg/day:
    - Trend for lower cumulative dose of steroids
    - No impact on secondary outcomes (benefit or adverse effect).

- Rash >50%, Stool > 1 Liter and/or Liver Involvement.
  - —**2mg/kg/day should remain the starting dose.**
    - No Reduction in Cumulative Dose
    - Worse secondary outcomes (much more likely to need secondary therapy and trend for progression to higher grade GVHD).

TARGETED THERAPY



* Source: NCI Dictionary of Cancer Terms

Target in acute GVHD: T-Cell Mediated Disease

- As a T-cell mediated disease, T cells are the logical “target”.
- Targeting T-cells is certainly not new:
  - ATG: Often used in SR-acute GVHD but even with response long-term survival is poor

Arai S, et al. Biol Blood Marrow Transplant 2002;8:155-60

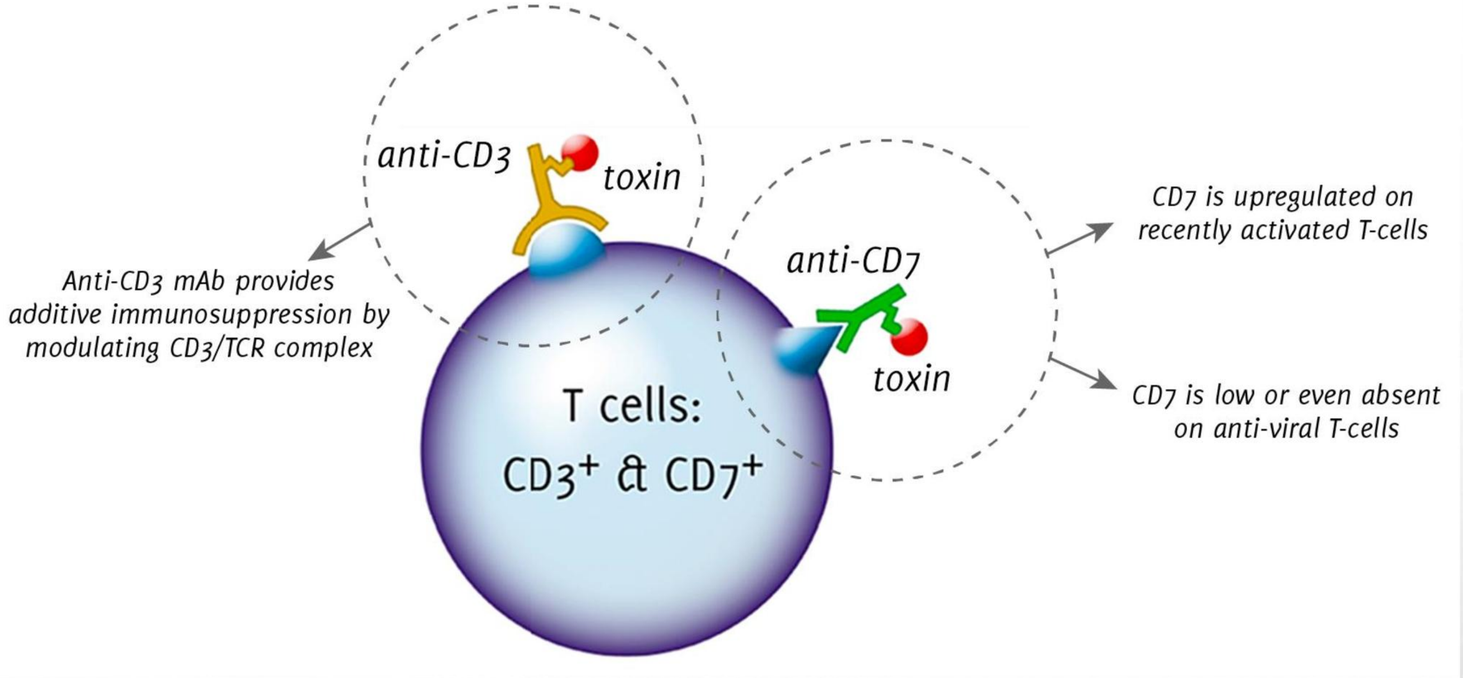
ASH Abstract 513. December 10th, 2017

A phase I/II study on the anti-CD3/CD7 immunotoxin combination (T-Guard) for the treatment of steroid-refractory acute GVHD

Christoph Groth, Lenneke F.J. van Groningen, Manita E.J. Bremmers, Frank W.M.B. Preijers, Harry Dolstra, Tiago R. Matos, Christian Reicherts, Eric G. van Hooren, Ypke V.J.M. van Oosterhout, John E. Levine, James L. Ferrara, Nicole M.A. Blijlevens, Matthias Stelljes, and Walter J.F.M. van der Velden

Novel Agent T-Guard

Combination of two immunotoxins: anti-CD3 and anti-CD7



CD-cluster of differentiation
mAb-monoclonal antibody
TCR-T-cell receptor

IT-combination T-Guard

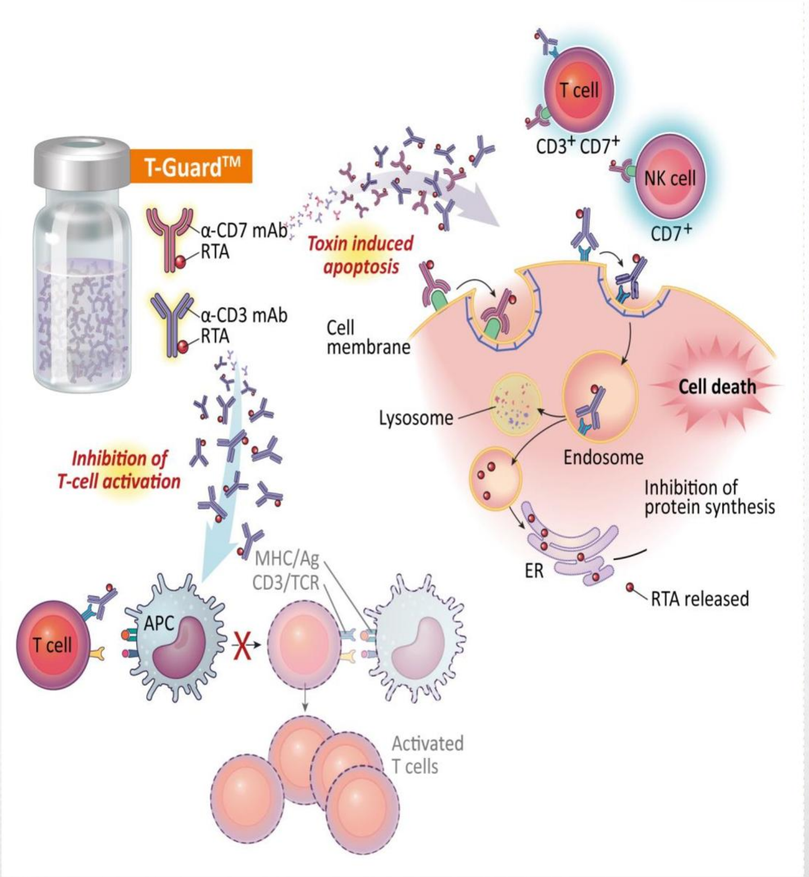
- IT-combination: murine anti-CD3 and anti-CD7 mAbs
  with a Ricin Toxin A chain (RTA) conjugate.

- Mechanism of action:
  - —*Synergistic in-vivo T- and NK-cell depletion.*
  - —*Blocking TCR activation (anti-CD3).*

- Relative specificity for activated T-cells (ratio 35:1).

- Short half-life: ≈ 7 hours.

- Dose-escalation study (*N*=7): 3rd-line therapy.
  - —*Safe and tolerable.*
  - —*Promising clinical responses (1 PR, 3 CR).*
  - —*Fast immunoreconstitution post T-Guard.*



NK- cell- natural killer cell; APC-antigen presenting cell; Ag-antigen
ER-endoplasmic reticulum; IT-immunotoxin
MHC-major histocompatibility complex; PR- partial response

Van Oosterhout Y, et al. Blood 2000;95:3693-3701

GVHD-related characteristics	N=20
SR-acute GVHD, grade	
- **Grade II**	3 (15%)
- **Grade III-IV**	17 (85%)
Organ involvement:	
- **2 organs involved**	16 (80%)
- **Intestinal involvement (GI-GVHD)**	18 (90%)
- **Liver involvement**	5 (25%)
Baseline albumin levels g/L	
- **Median (range)**	23 (16-34)
Biomarker panel (ST2/REG3α)*	
- **Intermediate risk ($\hat{p} < 0.08$)**	50%
- **High risk ($\hat{p} \geq 0.32$)**	50%
Time to T-Guard, days	8 (5-16)

*MAGIC consortium

Groth C, et al. Biol of Blood Marrow Transplant 2018; 00 1-8

Conclusions

- T-Guard safe and well tolerated.
- Encouraging Clinical Responses High CR rate (50%), encouraging 6-month OS .
- Swift immune reconstitution (cell count and T-cell diversity)
- Preservation of anti-viral T cell clones
- Results need confirming in larger, multicenter trial → BMT CTN 1802 (***non-randomized***, phase 3 for FDA approval).

Groth C, et al. Biol of Blood Marrow Transplant 2018; 00 1-8

Next Generation Therapies: Small Molecules and Biologics:

JAK-Inhibitors

JAK Inhibition

- Janus kinases serve to transduce extracellular signals from a number of cytokines and growth factors that are upregulated and thought to be involved in the pathogenesis of various inflammatory disease states.

Pre-Clinical GVHD Models

- Ruxolitinib treatment in mice resulted in less CXCR3 expression, reduced GVHD and improved survival after strain MM alloHCT.
- Effect was shown to be mediated by altered trafficking of T-cell to GVHD target organs.
- Other models suggested ruxolitinib impaired differentiation of CD4+T cells into interferon-Ɣ and IL-17A-producing cells which are critical to GVHD pathophysiology.
- Ruxolitinib treatment is also believed to increase FoxP3+ T regs in periphery and target tissues.
- Shown not to inhibit GVL in MRD mouse models (altered T-cell trafficking without affecting T-cell expansion).

Choi J, et al. PLoS ONE 2014;9:e109799
Carniti C, et al. Clin Cancer Res 2015;21:3740-49
Spoerl S, et al. Blood 2014;124:3934

CXCR3-chemokine receptors R3
MM-mismatch
alloHCT- allogeneic hematopoietic cell transplantation
FOXP3-forkhead box P3
Tregs-T regulatory cells
MRD-minimal residual disease

Clinical Data: Zeiser et al. *Multicenter Survey*

- Patients with severe aGVHD respond to ruxolitinib

- The overall response rate (ORR) was 81.5% (44/54) including 25 CRs (46.3%).
- The median time to response was 1.5 (1–11) weeks after initiation of ruxolitinib treatment.
- The 6-month survival estimate was 79% (67.3–90.7%, 95% CI).
- The median follow-up time was 26.5 (3–106) weeks for SR-aGVHD patients.
- Relapses in aGVHD occurred in 6.8% (3/44) of ruxolitinib-responsive patients (2 PR, 1 CR).

Zeiser R, et al. Leukemia 2015;29:2062-68

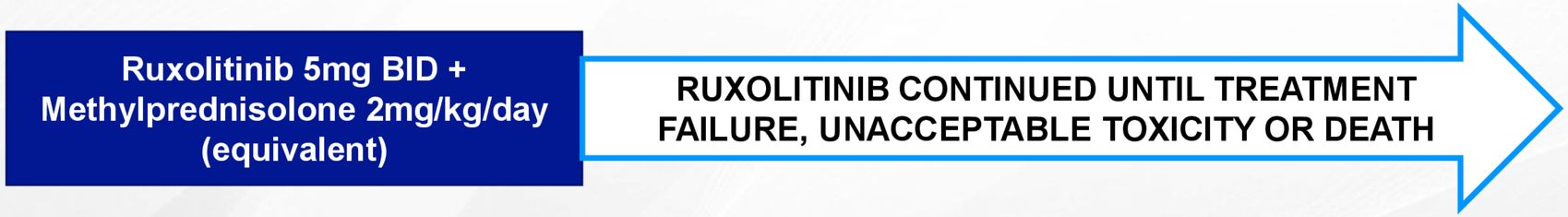
Conclusions Ruxolitinib

- **FDA Granted Ruxolitinib Breakthrough Designation for Acute GVHD based on Zeiser et al.**
- A Single-Cohort, Phase 2 Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease **(REACH1).**
- **GRAVITAS-301**: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Itacitinib or Placebo in Combination With Corticosteroids for the Treatment of First-Line Acute Graft-Versus-Host Disease.
- Additional Studies planned / being conducted.
- Exciting but needs formal testing!!!

REACH1 STUDY DESIGN:
Open-label, Multicenter, Phase 2 trial

- Eligibility: ≥12 years, first alloHCT, myeloid engraftment, SR-aGVHD who received ≤ 1 line of therapy beyond steroids.

- Treatment Scheme:



- Endpoints
  - —Primary: Day 28 Overall Response Rate (CR, VGPR, PR).
  - —Key Secondary: Duration of Response at 6 months.
  - —Other Secondary: NRM, Safety, Relapse Rate, OS

Jagasia M, et al. Blood 2018:132-601

VGPR-very good partial response

Next Generation Therapies: Small Molecules and Biologics:

Alpha-1- Antitrypsin

Alpha-1-antitrypsin (AAT) in acute GVHD

- Protease Inhibitor produced by the liver that inactivates several serine proteases from neutrophils and macrophages and protects tissues from proteolysis.
- AAT, derived from donated plasma, is most commonly used for patients with lung disease due to alpha-1 anti-trypsin deficiency.
- Recently found to play immune regulatory role independent from protease inhibition

Alpha-1-antitrypsin (AAT) in aGVHD

- AAT has been shown to attenuate severity of GVHD in murine models.
  - —Reduction of inflammatory cytokines
  - —Alterations in ratios of Effector/ regulatory T-cells.
  - —Reduction in Damage Associated Molecular Patterns (DAMPs).

- Patients with lower GI GVHD have been found to have increased stool losses of AAT and seem to correlate with steroid-resistance.

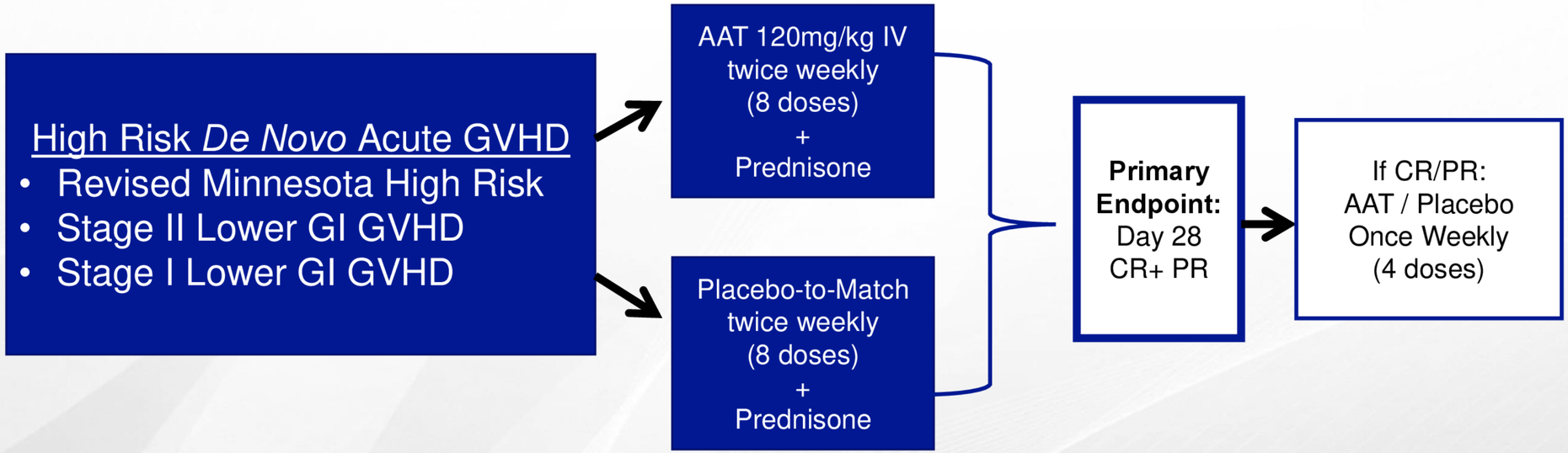
Tawara I, et al. PNAS 2012;109:564-69
Reddy P. Blood 2012;120:2780-2781
Marcondes AM, et al. Blood 2014;124:2881-91
Brennen et al. *Blood* 2012; 120: 2899-908
Weisdorf SA, et al. Gastroenterology 1983;85:1076-81.
O'Meara A, et al. Bone Marrow Transplantation 2015;50:1105-09
Rodriguez-Otero P, et al. Blood 2012;119:5909-17

Alpha-1-Anti-Trypsin (AAT): Pilot Phase I/II Trial

- A second trial phase I/II of AAT (Glassia; Baxalta/Kamada, New Ziona, Israel) as salvage therapy to 12 patients with SR-aGVHD.
  - —All patients had grades III or IV GVHD with stage 4 gut involvement.
  - —After treatment, plasma AAT levels increased and remained within 2 to 4 mg/mL for the duration of treatment.
  - —No clinically relevant toxicities attributable to AAT were observed.
  - —GVHD manifestations improved in 8 of 12 patients, and 4 responses were complete.
  - —Six patients (50%) were alive at last follow-up (>104 to >820 days).

Marondes AM, et al. Biol Blood Marrow Transplant 2016;22:1596-1601

Treatment Schema: BMT CTN1705
AAT in Patients with High-Risk Acute GVHD



National Protocol Chairs
John Magenau
Amin Alousi

Next Generation Therapies: Targeting High-risk GVHD Organ(s)

THERAPIES DIRECTED AT THE GASTROINTESTINAL TRACT

- Fecal Microbiota Transplant
- Anti-complement Therapy
- Alpha-1-antitrypsin (AAT)
- Recombinant IL-22
- Anti-integrins

Kakihana K, et al. Blood 2016; 128: 2083-88
DeFlipp Z, et al. Blood Adv 2018; 7: 745-53
Kwan WH, et al. J Clin Invest.2012; 6: 2234-8.
Magenau JM, et al. Blood 2018;131:1372-79
Marondes AM, et al. Biol Blood Marrow Transplant 2016;22:1596-1601

Hanash AM, et al. Immunity 2012; 2: 339-50
Lindemans CA, et al. Nature 2015; 528: 560-64
Kekre N, et al. Blood 2017;130:3252
Floisand Y, et al. Biol Blood Marrow Transplant 2017; 1: 172-75

Targeting the Gastrointestinal Tract

Anti-integrins

Role of α4β7+ integrin in the Pathophysiology of acute GVHD

- Priming and maturation of naïve donor T-cells that are targeted for the gut mucosa are believed to be mediated by activated host dendritic cells within gut associated lymphoid tissue (GALT).
- Evidence suggests that effector T cells acquire an intestinal homing phenotype.
- Once T-cells are educated in the GALT through antigen engagement and co-stimulation they continue to circulate through the bloodstream and migrate to intestinal effector sites of the LP in the small and large bowel.

Mora JR, et al. Nature 2003;424:88-93
Johansson-Lindbom B, et al. J Exp Med 2003;198:963-69
Hayday A, et al. Nature Immunology 2001;2:997-1003

A4β7-alpha 4 beta 7; LP-lamina propria

Role of α4β7+ integrin in the Pathophysiology of acute GVHD

- A4β7 integrin plays a crucial role in recirculation of naïve T-cells to GALT as well as selective trafficking of specific effector T cells into sites of intestinal inflammation.

- The primary ligand for α4β7+ integrin is mucosal addressin cell adhesion molecule 1 (MAdCAM-1) which is selectively expressed in endothelial venules and follicular dendritic cells of GALT with upregulation at sites of active inflammation.

Bargatze RF, et al. Immunity 1995;3:99-108
Rott LS, et al. J Immunol 1996;156:3727-3736
Berlin C, et al. Cell 1993;74:185-95
Nakache M, et al. Nature 1989;337:179-181

Abstract 3252: Phase II of Natalizumab with Corticosteroids as Initial Treatment of GI aGVHD

- Study Population: Patients with new-onset, Lower GI GVHD.
- Study Treatment: Natalizumab 300mg IV + Steroids.
- A total of 18 patients were enrolled.

Lower GI Stage	Number of Patients (n=18)
Stage 1	7
Stage 2	4
Stage 3	4
Stage 4	3
* 4 patients had concomitant skin, 1 liver	

Kekre N, et al. Blood 2017;130:3252

Abstract 3252: Phase II of Natalizumab with Corticosteroids as Initial Treatment of GI aGVHD

Endpoint	
Day 56 GVHD-Free Survival	37.5%
Day 28 Overall Response Rate	75%
Day 56 Overall Response Rate	62.5%
6-month Overall Survival	52%

Kekre N, et al. Blood 2017;130:3252

Abstract 3252: Phase II of Natalizumab with Corticosteroids as Initial Treatment of GI aGVHD

Toxicities	
Treatment Related Toxicity (potentially related)	N=1 Grade 2 hepatotoxicity N=1 Grade 4 Encephalopathy N=1 Grade 5 Hepatic failure
JC Viremia	Before Treatment: 6 patients After Treatment: 8 patients
JC- related Disease	No patients
Causes of Death	GVHD (N=2) Relapse (N=2) Organ Failure (N=3)

Kekre N, et al. Blood 2017;130:3252

Next Generation Therapies: Targeting High-risk GVHD Organ(s)

THERAPIES DIRECTED AT THE GASTROINTESTINAL TRACT

- Fecal Microbiota Transplant
- Anti-complement Therapy
- Alpha-1-antitrypsin (AAT)
- Recombinant IL-22
- Anti-integrins

Kakihana K, et al. Blood 2016; 128: 2083-88
DeFlipp Z, et al. Blood Adv 2018; 7: 745-53
Kwan WH, et al. J Clin Invest.2012; 6: 2234-8.
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Marondes AM, et al. Biol Blood Marrow Transplant 2016;22:1596-1601

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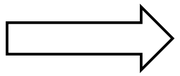
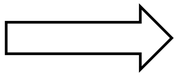
Kekre N, et al. Blood 2017;130:3252
Floisand Y, et al. Biol Blood Marrow Transplant 2017; 1: 172-75

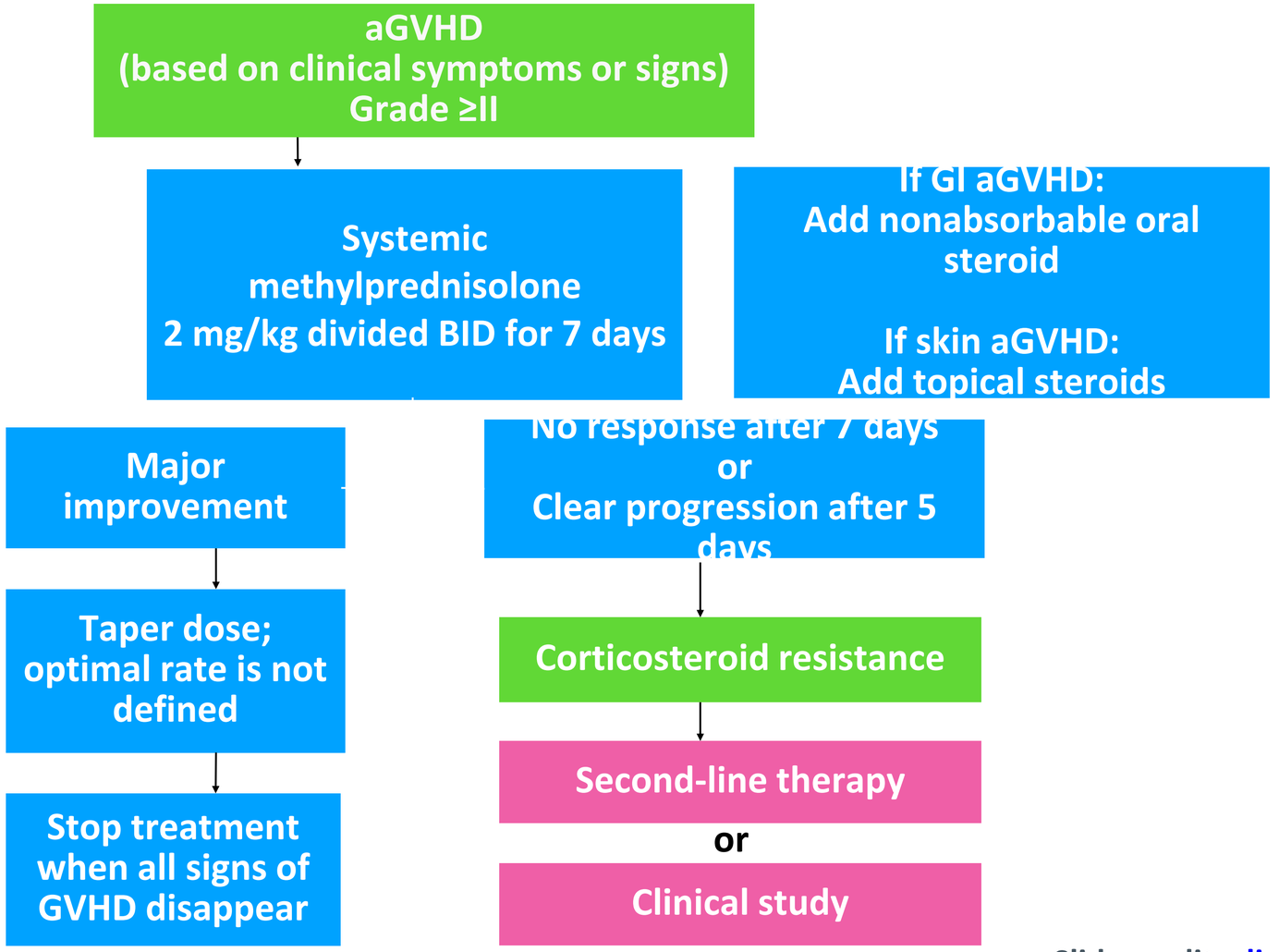
EBMT/ELN Treatment Guidelines for Acute GVHD

Gold standard is systemic steroid therapy



Taper steroid doses as soon as major improvement is seen



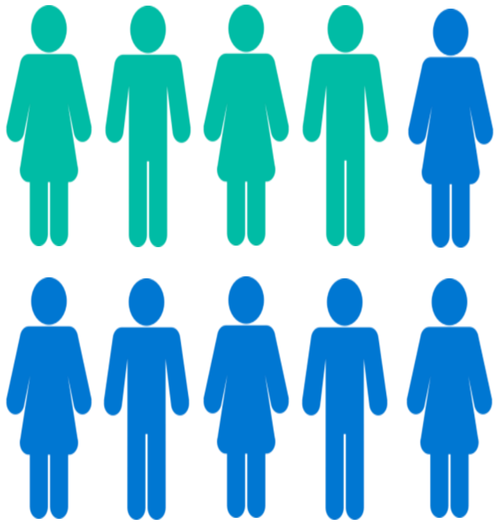


Penack. Lancet Haematol. 2020;7:e157.

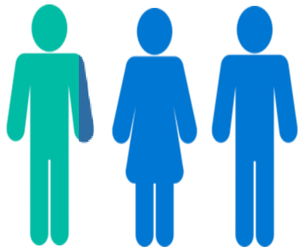
Slide credit: clinicaloptions.com

Response to Steroids in Patients With aGVHD

Steroids are effective in **only 40%** of patients with aGVHD



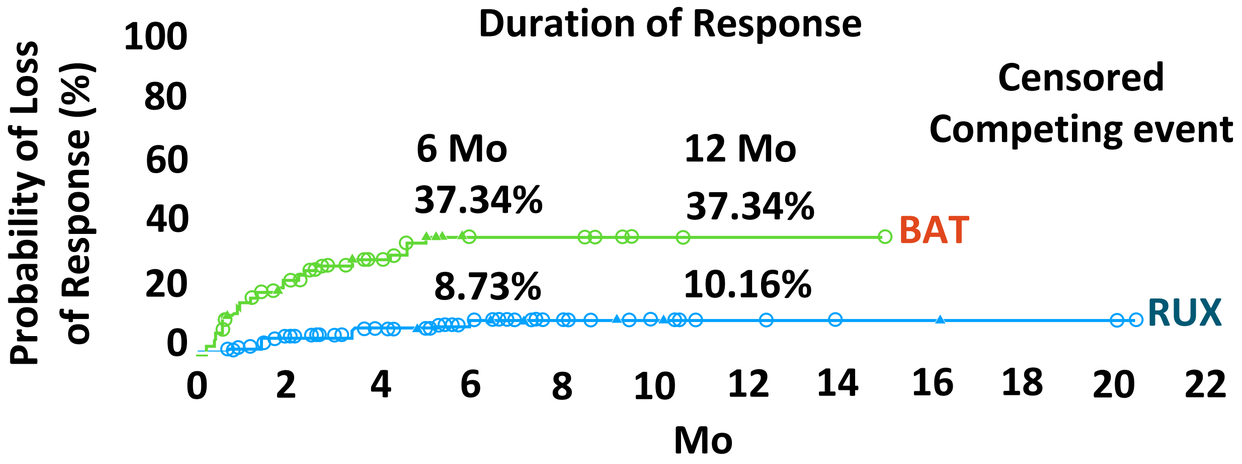
Only 30% of patients with aGVHD have a long-lasting response to steroids

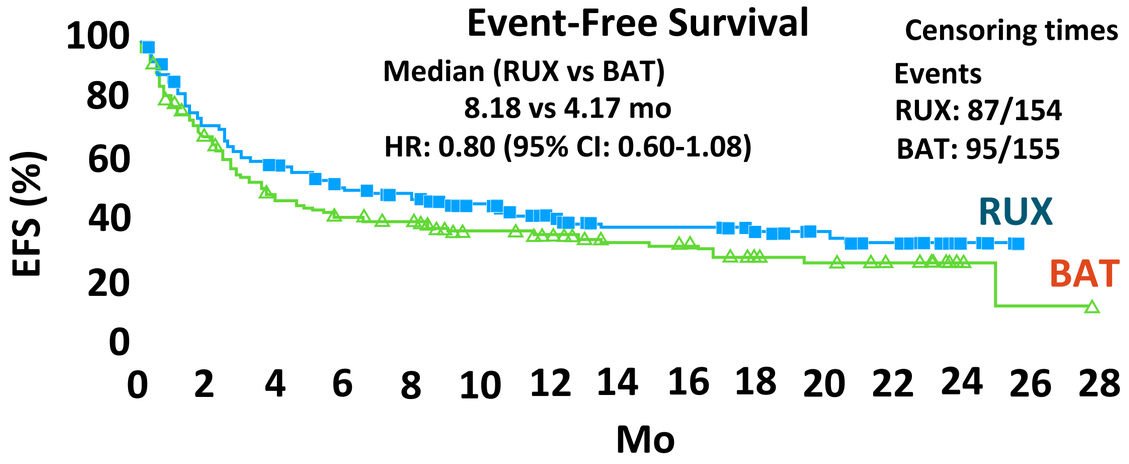


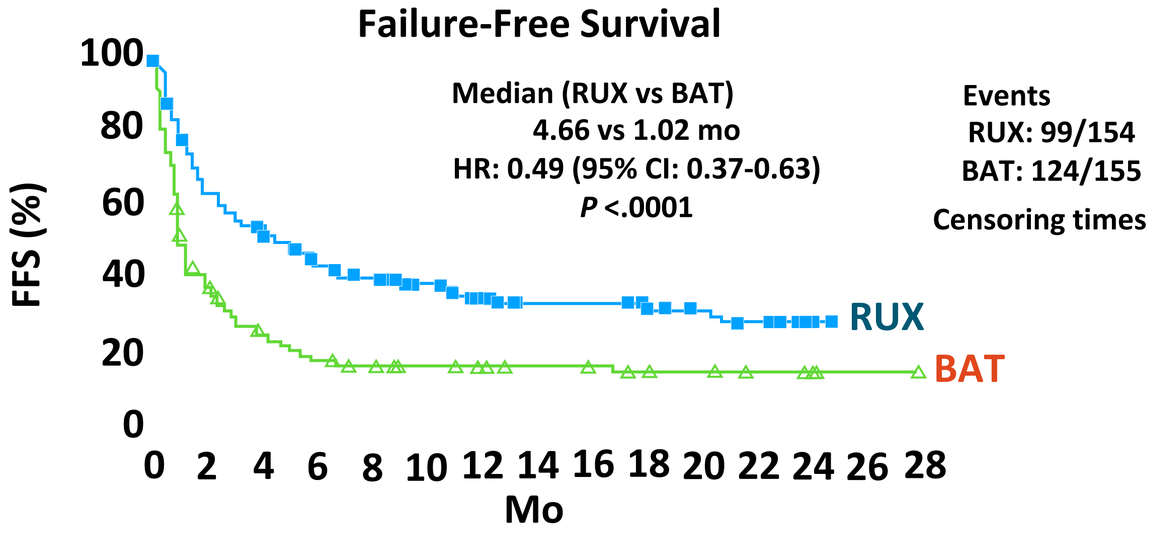
Murray. The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT. 2018:221-251.

Slide credit: clinicaloptions.com

REACH 2: DoR and Survival in Patients with Acute GVHD Treated With Ruxolitinib vs Best Available Therapy







Mohty. EBMT 2021. Abstr O067.

Slide credit: clinicaloptions.com

Chronic GVHD: The Bane of Allogeneic Transplantation

- **>50% incidence following related and unrelated alloHCT**
  - Incidence increasing as aGVHD outcomes improve
- **Most important cause of morbidity following alloHCT**
  - Affects quality of life and causes irreversible functional deficits
  - Most have ≥1 organ system involved
  - Median 2-3 yr of treatment
  - <80% of patients with cGVHD come off immune suppression

Ratanatharathorn. Bone Marrow Transplant. 2001;28:121. Steward. Blood. 2004;104:3501.

Slide credit: clinicaloptions.com

Initial Treatment in Chronic GVHD: Corticosteroids

- Systemic symptoms or multiple local sites → systemic treatment
- Initial treatment:
  - Prednisone: 1 mg/kg/day
  - Tacrolimus: 5-10 ng/mL *or*
  - Cyclosporine: 200-400 µg/L
- Complete response rate: 50% to 55%
- Median time to discontinue immune therapy: 1.6-2.2 yr
- Additional agents at onset of GVHD: Not shown to be beneficial

Arora. Biol Blood Marrow Transplant. 2001;7:265. Koc. Blood. 2002;100:48.

Ibrutinib Treatment for Chronic GVHD

- Ibrutinib resulted in clinically meaningful and sustained responses in patients who have failed ≥1 prior treatment for cGVHD
  - ORR: 67%
  - 71% had a sustained response of ≥20 wk
  - Similar response rate across all affected organs
- Patients experienced reductions in corticosteroid doses while receiving ibrutinib
- Biomarker changes support a beneficial effect of ibrutinib on cGVHD-related immune cell subsets
- AEs are consistent with those previously reported for ibrutinib and those observed in patients with cGVHD receiving concomitant corticosteroids
- **Efficacy of ibrutinib in this population supported FDA approval of ibrutinib for patients with established cGVHD requiring additional therapy in August 2017**

Miklos. Blood. 2017;130:2243. Ibrutinib PI.

Slide credit: clinicaloptions.com

Phase III Trials for Treatment of Steroid-Refractory Chronic GVHD

Arms	Estimated N	Patient Characteristics	Trial Identifier(s)	Primary Endpoint	
Ruxolitinib vs best available therapy	329	Steroid-refractory moderate or severe GVHD	NCT03112603 REACH3	Response rate at cycle 7 (Wk 24)	Zeiser NEJM 2021

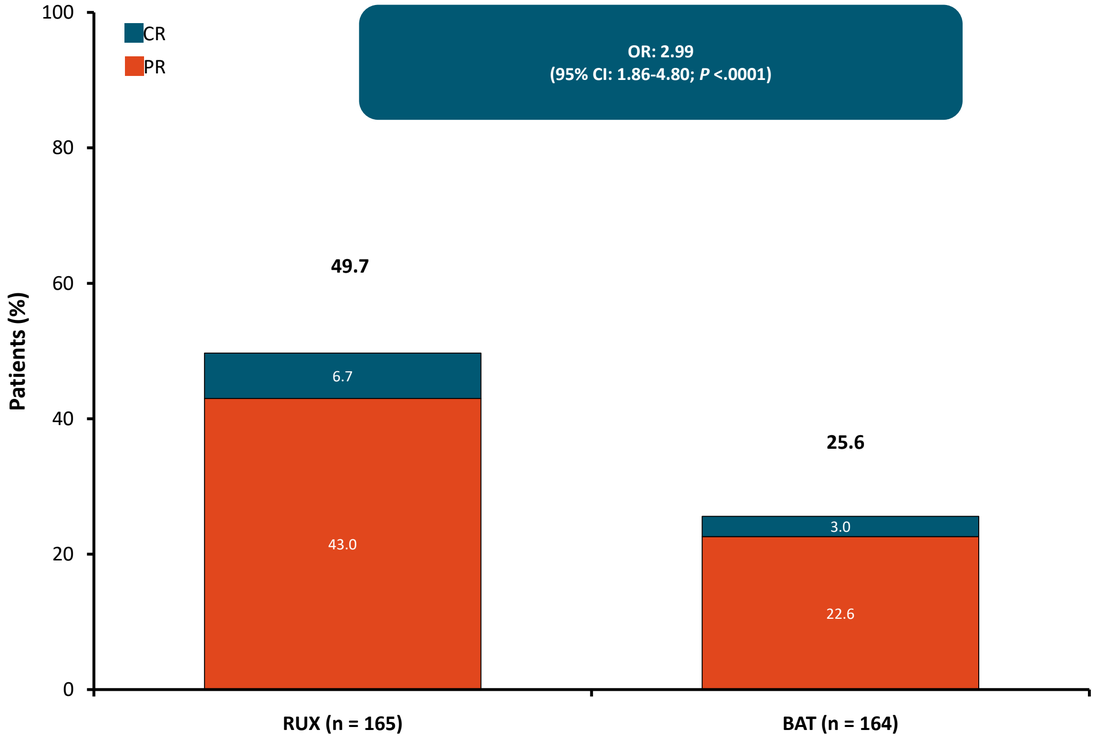
Another notable phase III trial for prevention of cGVHD

Arms	Estimated N	Patient Characteristics	Trial Identifier(s)	Primary Endpoint	
CD34-selected T-cell depletion in PBSC grafts vs PTCy vs tacrolimus + MTX	346	Prophylaxis in patients undergoing HSCT from matched related donor or unrelated donor	NCT02345850 BMT CTN 1301 PROGRESS-II	cGVHD-free relapse-free survival at 2 yr	Luznik JCO 2021

Zeiser. NEJM. 2021;385:228. Cutler. Blood. 2021;38:2278. Luznik. JCO. 2021;[Epub].

Slide credit: clinicaloptions.com

REACH3: ORR at Wk 24 in Patients With Steroid-Refractory Chronic GVHD Treated With Ruxolitinib



Characteristic, n (%)	RUX (n = 165)	BAT (n = 164)
Responders	82 (49.7)	42 (25.6)
▪CR	11 (6.7)	5 (3.0)
▪PR	71 (43.0)	37 (22.6)
Nonresponders		
Unchanged response	9 (5.5)	15 (9.1)
Mixed response	10 (6.1)	17 (10.4)
Progression	4 (2.4)	21 (12.8)
Other*	5 (3.0)	9 (5.5)
Unknown†	55 (33.3)	60 (36.6)

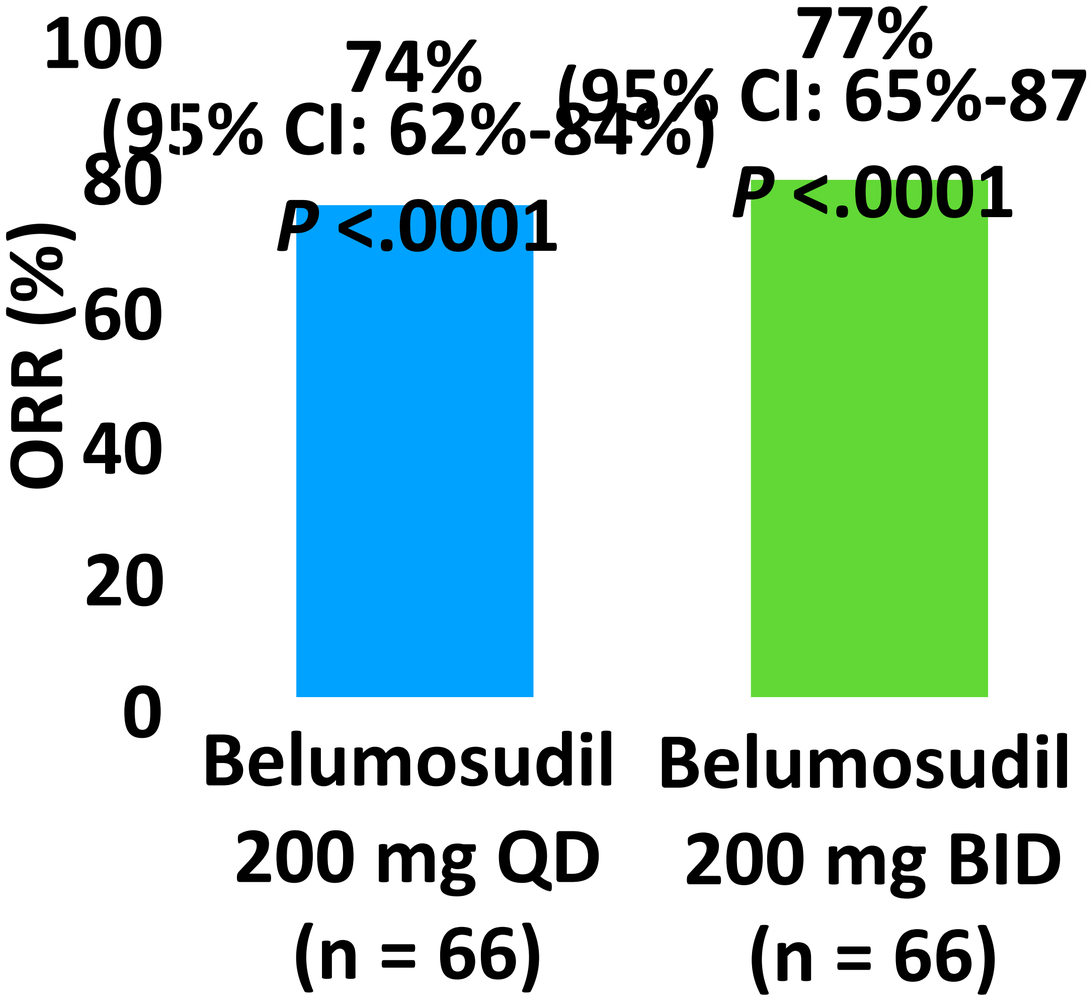
***Patients with additional systemic therapies and investigator-assessed CR/PR. †Death, early discontinuation, or missing data.**

- ORR was significantly higher with RUX
- **FDA approved ruxolitinib 10 mg BID for treatment of cGVHD after failure of 1-2 prior lines of systemic therapy in adults and pediatric patients 12 yr of age or older (9/22/21)**

Zeiser. NEJM. 2021;385:228. Ruxolitinib PI.

Slide credit: clinicaloptions.com

ROCKstar: ORR in Patients With Steroid-Refractory Chronic GVHD Treated With Belumosudil



- Median time to response: 5 wk (range: 4-66)
- Prespecified statistical significance was achieved as lower bound of the 95% CI of ORR exceeded 30%
- **FDA approved belumosudil 200 mg daily for treatment of cGVHD after failure of ≥2 prior lines of systemic therapy (7/16/21)**

Cutler. Blood. 2021;38:2278. Belumosudil PI.

Slide credit: clinicaloptions.com

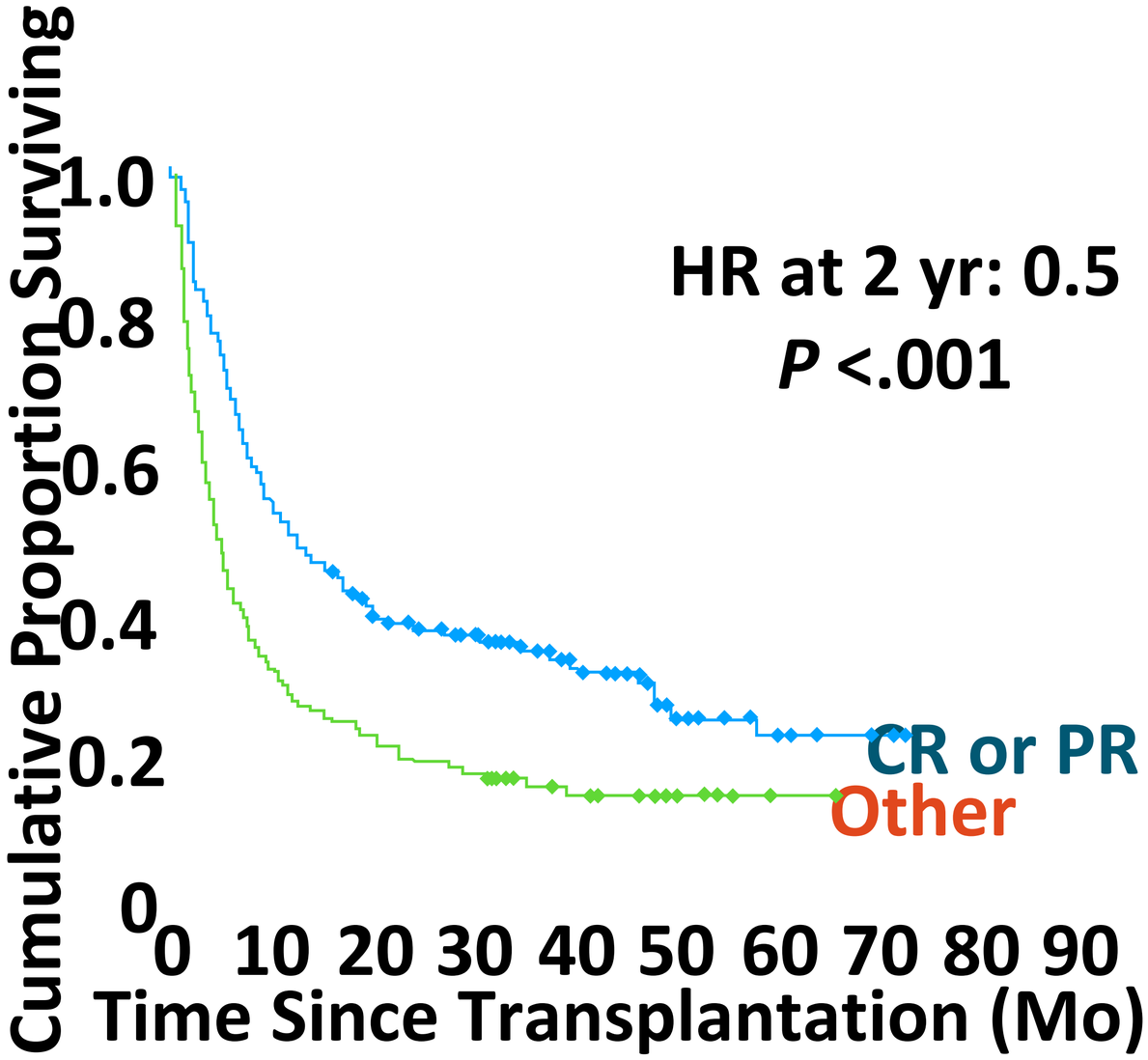
Chronic GVHD With HCT: Conclusions

- cGVHD is clinically heterogeneous and pathogenesis complex involving dysregulated B-cells and T-cells due to alloreactive damage to thymus, BM, and germinal centers; cGVHD pathogenesis involves macrophage mediated fibrosis
- FDA approved for cGVHD treatment after ≥1 line of therapy:
  - Ibrutinib 420 mg/day
    - Irreversibly inhibits activated B-cells and TFH cells inhibiting GC and allo-antibodies
    - PCYC1129: Ibrutinib 67% ORR at 1 yr and 31% CR at 2-yr follow-up
  - Ruxolitinib 10 mg twice daily
    - Inhibits STAT3 decreasing Th17 cells; decreased IL17 and TGF-ß decreases macrophage fibrosis
    - REACH3: ruxolitinib with higher ORR at Wk 24 than BAT (49.7% vs 25.6%; *P* <.0001)
- FDA approved for cGVHD treatment after ≥2 lines of therapy:
  - Belumosudil 200 mg/day
    - Inhibits Th17 cells, IL-21 secretion, regulates profibrotic genes and mediates stress fiber formation.
    - Phase II ROCKstar: belumosudil ORR: 74% with daily dosing (200 mg BID ORR: 77%)

Sahaf. Biol Blood Marrow Transplant. 2018;24:S20. Gomez-Rodriguez. FEBS J. 2011;278:1980. Miklos. Blood. 2017;130:2243. Ibrutinib PI. Chao. NEJM. 2020;382:1853. Zeiser. NEJM. 2021;385:228. Ruxolitinib PI. Cutler. Blood. 2021;38:2278. Belumosudil PI.

Does GVHD Impact Survival?

Overall Survival in Steroid-Responsive and Steroid-Refractory aGVHD



Westin. Adv Hematol. 2011;2011:601953.

Slide credit: clinicaloptions.com

Safety and Efficacy of Ruxolitinib vs BAT in Patients With SR aGVHD: REACH2 Phase III Study Design

- Multicenter, open-label, randomized trial

Patients ≥12 yr of age with grade II, III/IV SR aGVHD; evidence indicating myeloid engraftment with ANC >1000/mm^3 and platelets ≥20,000/mm^3 (N = 309)

Ruxolitinib 10 mg BID + steroids ± calcineurin inhibitors (n = 154)	**Ruxolitinib 10 mg BID + steroids ± calcineurin inhibitors**	**At 6 mo: Secondary analysis for OS and NRM**
BAT* + steroids ± calcineurin inhibitors (n = 155)	**BAT + steroids ± calcineurin inhibitors**	

***Patients randomized to BAT arm could cross over to ruxolitinib arm if primary endpoint not attained or response lost with disease progression, mixed response, or no response and requiring further systemic immunosuppressive therapy.**

- **Primary endpoint: ORR at Day 28**
- **Key secondary endpoint: durable ORR at Day 56**

Zeiser. NEJM. 2020;382:1800.

Slide credit: clinicaloptions.com

Urinary-Derived Human Chorionic Gonadotropin/ Epidermal Growth Factor for aGVHD: Study Design

- Prospective phase II trial

Patients with life-threatening aGVHD; creatinine <2.5x ULN; LVEF ≥35%

First line: Minnesota High Risk

uhCG/EGF 2000 units/m^2 SC every other day x 7 days + High-dose steroids* (n = 22)

Second line: no response to first line or GVHD flare

uhCG/EGF 2000 units/m^2 SC (steroid dependent) or 5000 units/m^2 SC (steroid refractory) every other day x 14 days + SoC immunosuppression* (n = 22)

***Responders eligible to receive optional maintenance doses twice weekly x 5 wk.**

- **Primary outcome: Day 28 response**
- **Secondary outcomes: safety, survival, exploratory metabolomics analysis, biomarkers**

Holtan. ASH 2021. Abstr 261. NCT02525029.

Slide credit: clinicaloptions.com

uhCG/EGF for aGVHD: Baseline Characteristics

Characteristic	First-line High Risk (n = 22)	Second Line (n = 22)
Median age, yr (range)	61 (22-72)	62 (2-69)
Median Karnofsky score (range)	60 (30-90)	50 (20-100)
Male, n (%)	16 (73)	17 (77)
Graft source, n (%)		
Marrow	5 (23)	8 (36)
Peripheral blood stem calls	8 (36)	9 (41)
Umbilical cord	9 (41)	5 (23)
Conditioning, n (%)		
▪Myeloablative	10 (45)	5 (23)
▪Reduced intensity	12 (55)	17 (77)
Median post-transplant day of enrollment, n (IQR)	57 (34-118)	123 (76-209)

Holtan. ASH 2021. Abstr 261.

Slide credit: clinicaloptions.com

uhCG/EGF for aGVHD: Day 28 Response (Primary Outcome) and Survival Outcomes

Outcome, n (%)	First-line High Risk (n = 22)	Second Line (n = 22)	All Patients (N = 44)
CR	64	50	57
PR	0	23	11

- Median OS for entire cohort: 1.2 yr
- 2-yr survival 67% vs 12% for responders vs nonresponders, respectively; *P* <.01

Holtan. ASH 2021. Abstr 261.

Conclusions

- There is evidence that acute GVHD affects not only the intestinal tract, liver, and skin, but also the CNS, thymus, ovaries, and multiple other organs
- 2-yr OS of patients with steroid-refractory acute GVHD is below 40%
- Ruxolitinib was approved by the FDA for SR-aGVHD in 2020
- Amphiregulin is promising as an aGVHD biomarker
- Novel regenerative approaches such as IL-22 and GLP-2 treatment in addition to immunosuppression may help improve the outcome of patients with SR-aGVHD

Indication of Biopsy in aGVHD

- when GVHD is diagnosed and treated, a confidence level of probable or confirmed can be assigned during the first 2 weeks post-transplant depending on whether GVHD is biopsy-proven.

- We therefore only diagnose liver GVHD manifesting as transaminitis without concomitant elevation in serum bilirubin when the presence of GVHD is confirmed by liver biopsy and score it as stage 0

- if bilirubin levels were elevated before the diagnosis of GVHD in another target organ and do not increase further, we do not diagnose liver GVHD in the absence of biopsy confirmation

BIOPSY INTERPRETATION

- Biopsies are often obtained to confirm a GVHD diagnosis, but experienced pathologists from different centers disagree on the threshold of histopathologic findings that should be present to diagnose acute GVHD

- Biopsy interpretation can be further complicated by the timing of the biopsy post- transplant and by the setting in which the symptoms arise and may not clearly identify the etiology of GVHD-like symptoms in up to 60% of biopsies

- These inconsistencies can result in highly variable treatment decision-making among clinicians

Risk-adapted initial treatment

- 1-For patients with grade 2a manifestations of aGHVD (defined as upper- GI symptoms, stool output <1L/d, rash <50% BSA, with-out hepatic involvement):
  treatment with lower- dose steroids (0.5mg/kg/d vs 1.0mg/kg/d) has been shown to be effective without increasing the risk of secondary immunosuppression.

- for patients with grade 2b or higher manifestations (defined as stool volume ≥1L/d, rash ≥50% BSA, or hepatic involvement):
  treatment with lower -dose steroids (1.0mg/kg/d vs 2.0mg/kg/d) was associated with an increased likelihood of requiring secondary immunosuppressive therapy.

- Recently, the BMT CTN reported (trial 1501) a randomized phase 2 study testing the steroid -free initial treatment of Minne-sota standard risk aGVHD (*N*=127) with sirolimus vs prednisone

- Although different doses and schedules have been used, the most widely used is methylprednisolone 2 mg/kg per day in divided doses.

- Steroids are continued for several weeks in responders and then gradually tapered over a period of several months. Gradual tapering is important to prevent a flare of GVHD.

- Patients who demonstrate progression of disease by day 5 or nonresponse by day 7 are considered to have corticosteroid resistance.

Case Presentation 1 : An adolescent (21 year old) male patient with acute lymphoblastic leukemia (ALL) Post-HSCT/ Acute GvHD

- On day +5 after recieving Methylprednisolon (+26 post transplant):
  Skin GvHD stage II
  Watery and bloody diarrhea, 7 times/day (1600 cc)

DDX: GI GvHD or CMV Colitis?

Case Presentation 1 : An adolescent (21 year old) male patient with acute lymphoblastic leukemia (ALL) Post-HSCT/ Acute GvHD

- CMV viral load by PCR Quantitative: 980 copies/ml
  Gancyclovir

- Rectosigmoidoscopy and biopsy
- Stool exam/culture/c. Diff

Next step? Wait for pathology or second line GvHD Treatment?
Continue Methylprednisolon?

SR-aGVHD (steroid -resistant) **definition/**

Steroid- dependent” aGVHD

SR-aGVHD (steroid -resistant) definition?

- progression of aGVHD within 3 to 5 days of treatment with ≥2mg/kg/d prednisone equivalent
- Or failure to improve with 5 to 7 days of treatment
- or incomplete response after more than 28 days of immunosuppres-sive therapy including steroids
- SR- aGVHD has also been recog-nized as
- (a) worsening GVHD manifestations in patients receiving ≥1mg/kg/d prednisone equivalent ≥2 days prior to steroid dose tapering;
- (b) persistent grade 2 to 4 GVHD without improvement ≥7 days during continued treatment with >0.4mg/kg/d predni-sone equivalent,
- (c) initial improvement followed by exacer-bation ≥3 days during steroid taper at any dose of >0.4mg/kg/d prednisone equivalent

Treatment options for SR-aGVHD

- ruxolitinib, an inhibitor of Janus kinase 1 and 2, for pediatric and adult patients 12 years of age or older . A starting dose of ruxolitinib, 5mg twice daily, was administered with methylprednisolone.

- At day 28, the over-all response rate (ORR) was 55%, durable day-56 ORR was also higher

- Ruxolitinib was associated with a higher incidence of thrombocy-topenia and a modest increase in anemia and cytomegalovirus infection.

TREATMENT OF RESISTANT DISEASE

- Ruxolitinib, rather than other agents, such as mycophenolate mofetil, etanercept, extracorporeal photopheresis,anti-thymocyte globulin, alpha-1 antitrypsin, mesenchymal stromal cells, everolimus, or sirolimus, based on superior efficacy and modest toxicity in a phase 3 trial comparing ruxolitinib with best available therapy (BAT)

- Gene expression studies from human colorectal biopsies showed that human SR -aGVHD is characterized by:
  -tis-sue response to damage, cellular stress, and macrophage accu-mulation, not T-cell proliferation

- these recent studies suggest that future therapeutic efforts in SR -aGVHD, in addition to targeting the initial T-cell -mediated damage and inflammation, might also consider studies of agents designed to enhance tissue repair and to correct dysbiosis while trying to avoid broad immunosuppression and its inherent risks of infec-tion.

- Recently described targets such as CD83 suggest this may be feasible.

Steroid- dependent” aGVHD

- (a) only achieving a par-tial (not complete) response to steroids after 8 weeks,
- (b) still requiring >10mg/m2 prednisone after 8 weeks or any prednisone at all after 10 weeks,
- or (c) a flare of aGVHD symptoms requiring at least a 25% increase in prednisone dose.

- experienced by 31% of patients with aGVHD.
- not associated with increased mortality, it may be associated with morbidity and a prolonged health care burden

Case Presentation 1 : An adolescent (21year old) male patient with acute lymphoblastic leukemia (ALL) Post-HSCT/ Acute GvHD

- Mycophenolate mofetil (15 mg/kg/BID)

- On day +30 post transplant (+5 post Mycophenolate mofetil):
  Skin GvHD stage I
  Lower GI GvHD stage II

- Pathology of rectosigmoid biopsy confirmed GvHD

Case Presentation 1 : An adolescent (21 year old) male patient with acute lymphoblastic leukemia (ALL) Post-HSCT/ Acute GvHD

- On day +35 post transplant (+10 post Mycophenolate mofetil):
  Skin GvHD stage 0
  Lower GI GvHD stage II

- Methylprednisolon tapered off

Case Presentation 1 : An adolescent (17 year old) male patient with acute lymphoblastic leukemia (ALL) Post-HSCT/ Acute GvHD

- On day On day +38 post transplant (+15 post Mycophenolate mofetil):

Skin GvHD stage 0
Lower GI GvHD stage 0

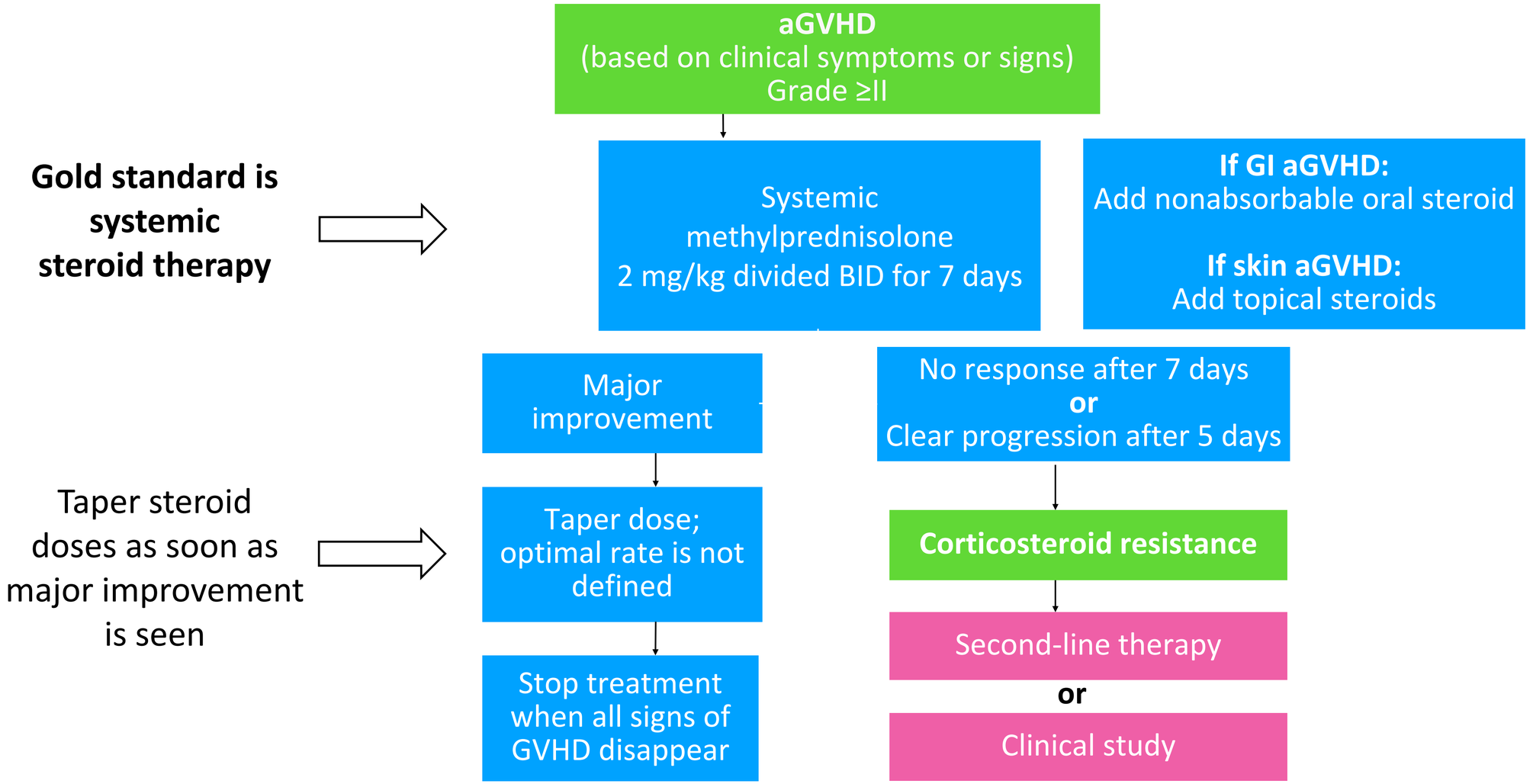
Dr. BIGLARY

The Twelfth Annual
Medical and Nursing Congress
in Hematopoietic Stem Cell Transplantation
Tehran Heart Center Hospital, Conference Hall, Tehran, IRAN
March 02-04, 2023

Management of Acute GVHD

Mohammad Biglari MD, MSc
Assistant Professor of Hematology, Medical Oncology & Bone Marrow Transplant
Research Institute for Oncology, Hematology & Cell Therapy
Tehran University of Medical Sciences
SAAWP of EBMT

EBMT/ELN Treatment Guidelines for Acute GVHD



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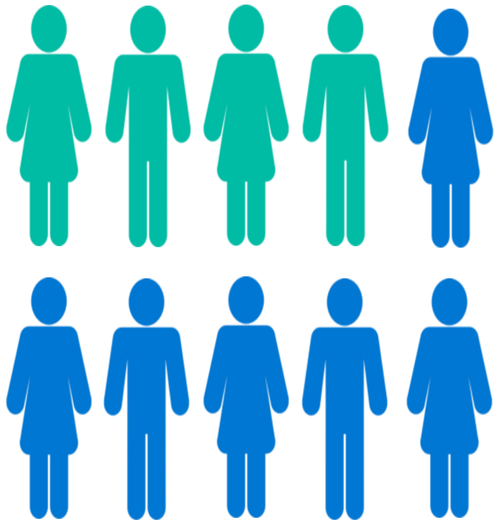

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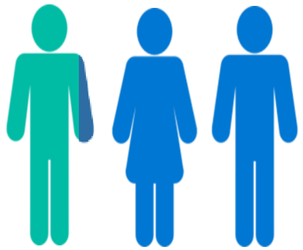
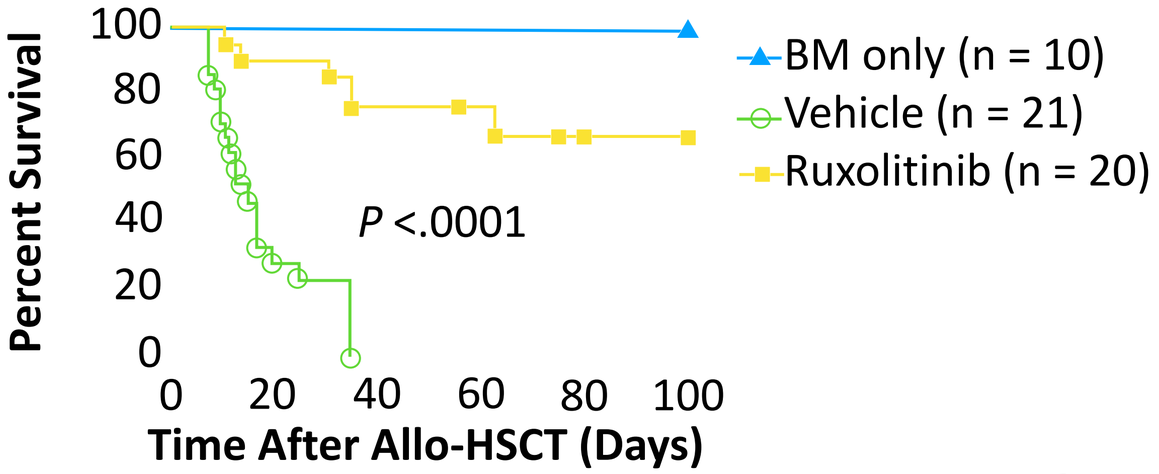
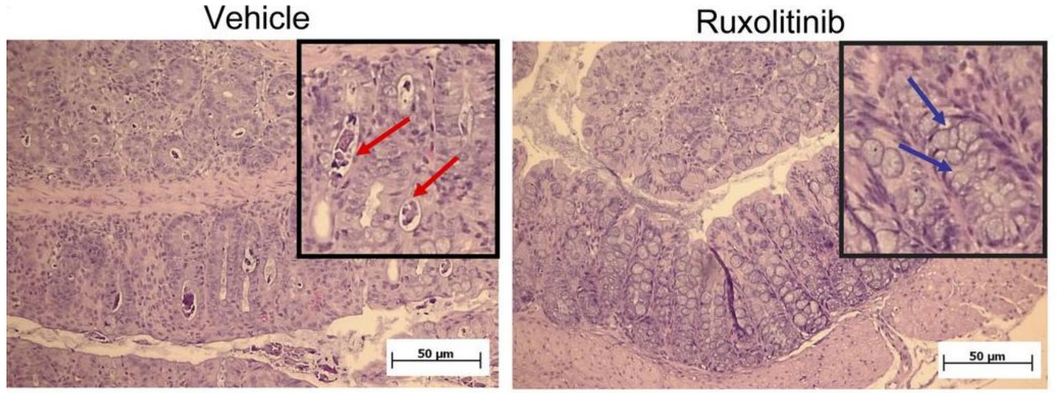
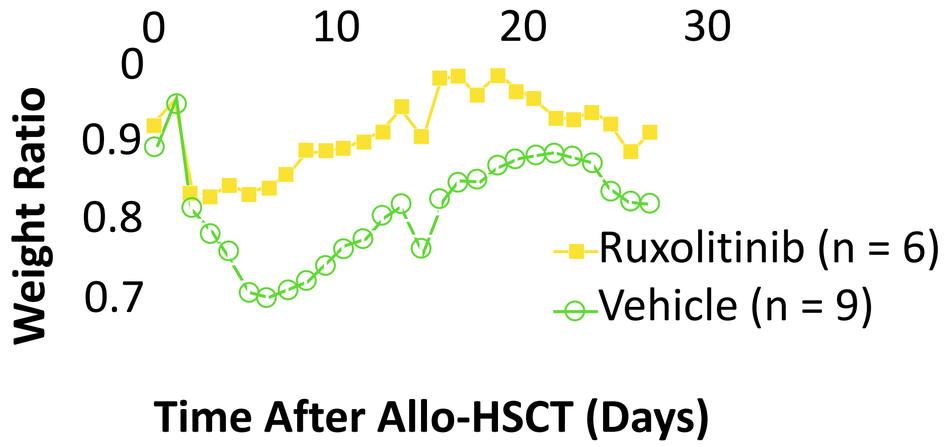


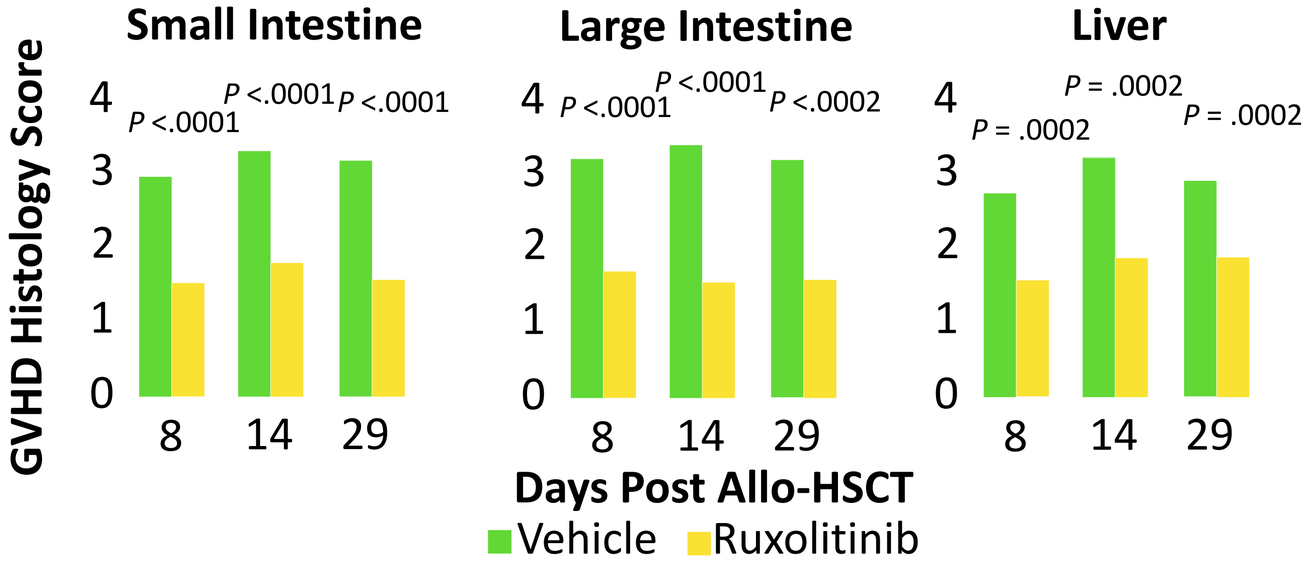
Murray. The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT. 2018:221-251.

Can We Reduce GVHD by JAK1/2 Targeting?









Spoerl. Blood 2014;123:3832.

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BAT + steroids ± calcineurin inhibitors

At 6 mo: Secondary analysis for OS and NRM

[redacted]

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Zeiser. NEJM. 2020;382:1800.

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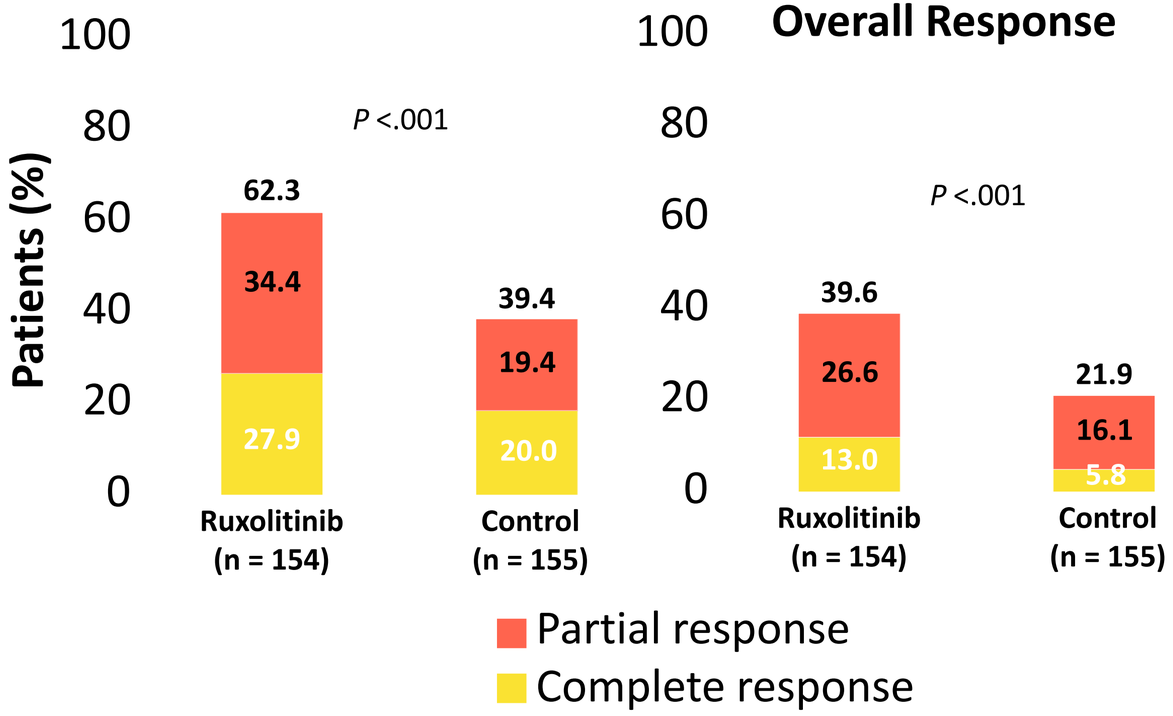
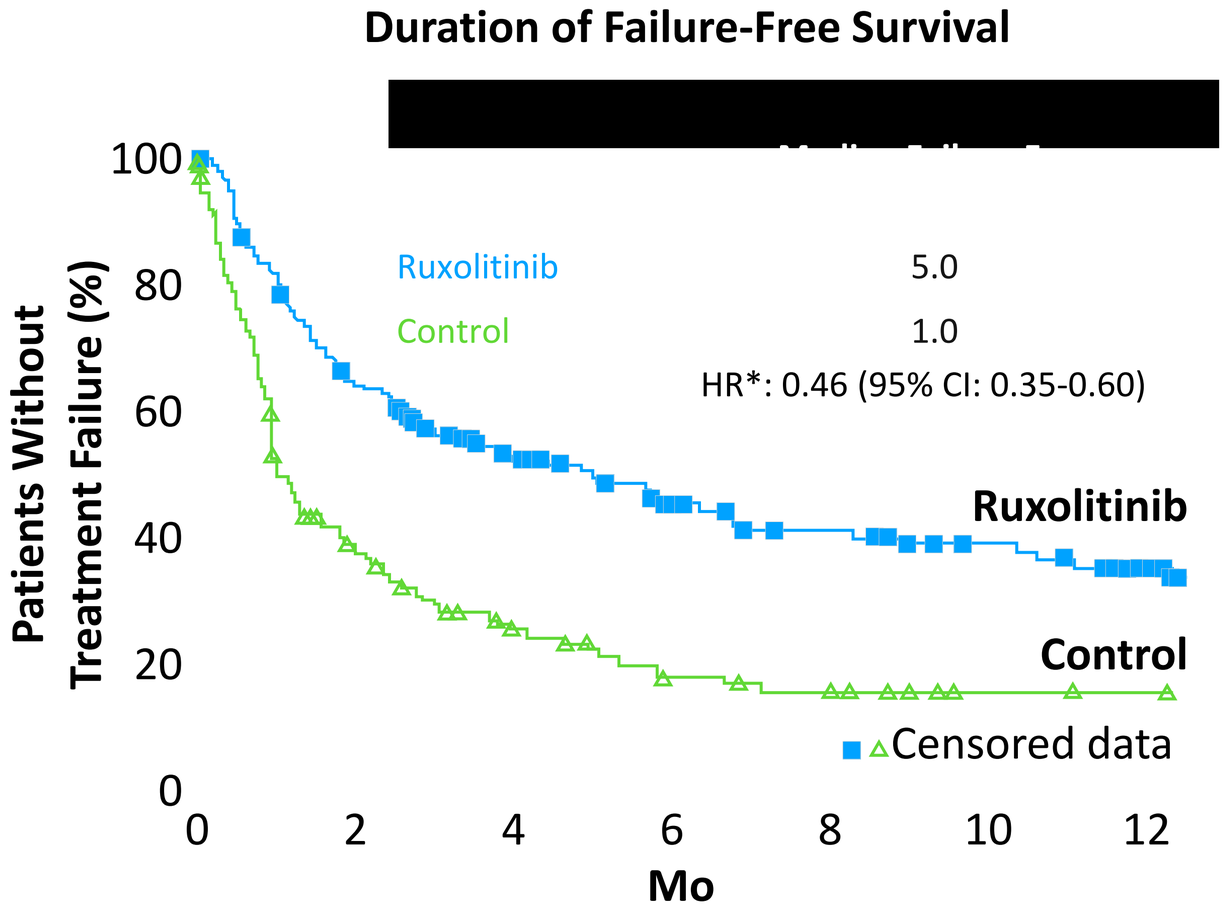
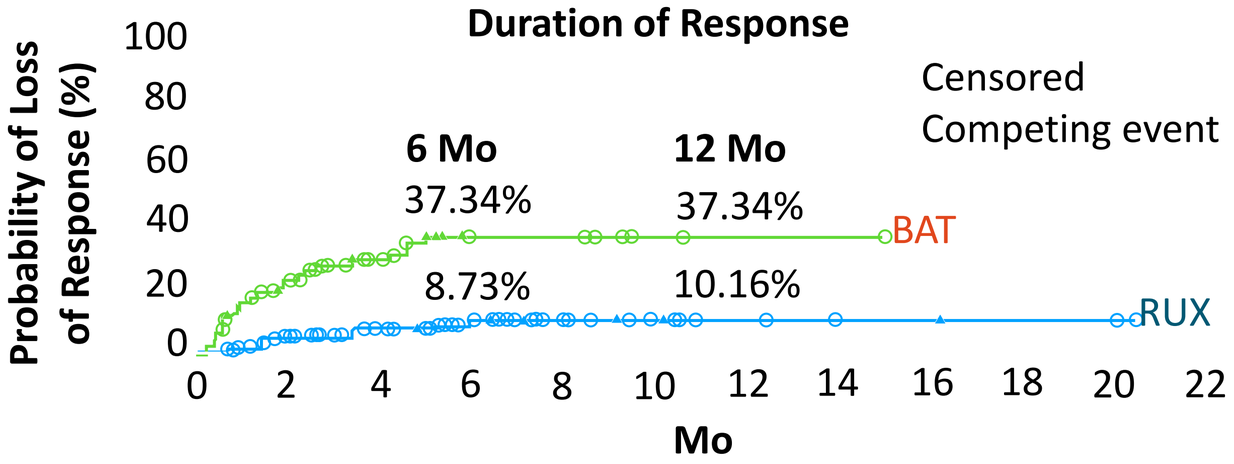


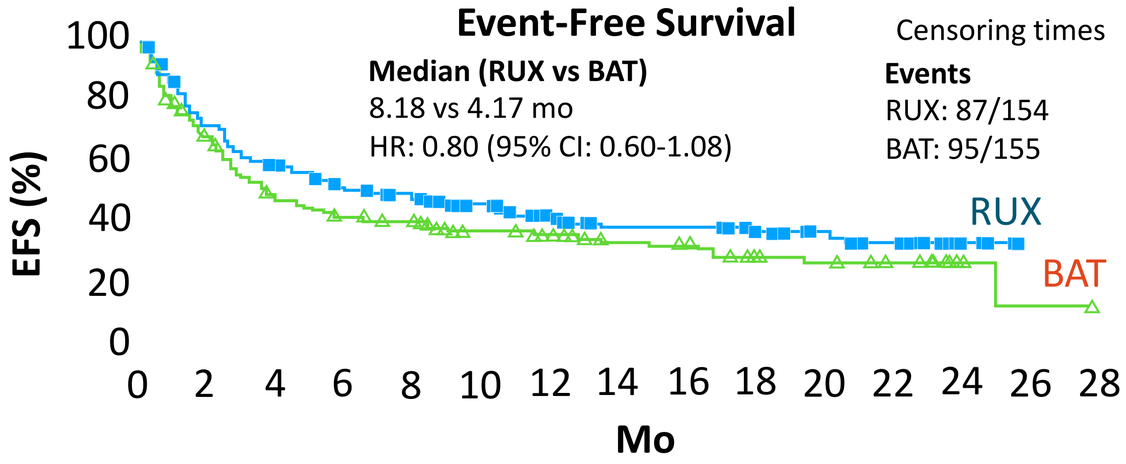


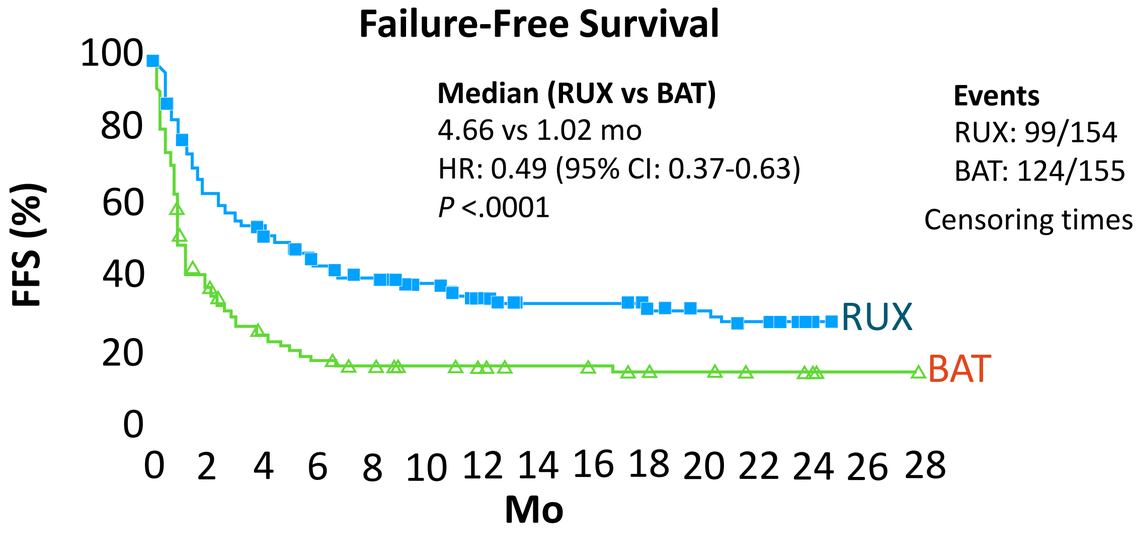
*HR for relapse or hematologic disease progression, non–relapse-related death, or additional new systemic therapy for aGVHD.

Zeiser. NEJM. 2020;382:1800.

REACH 2: 6-Mo Follow-Up
Duration of Response and Event-Free Survival



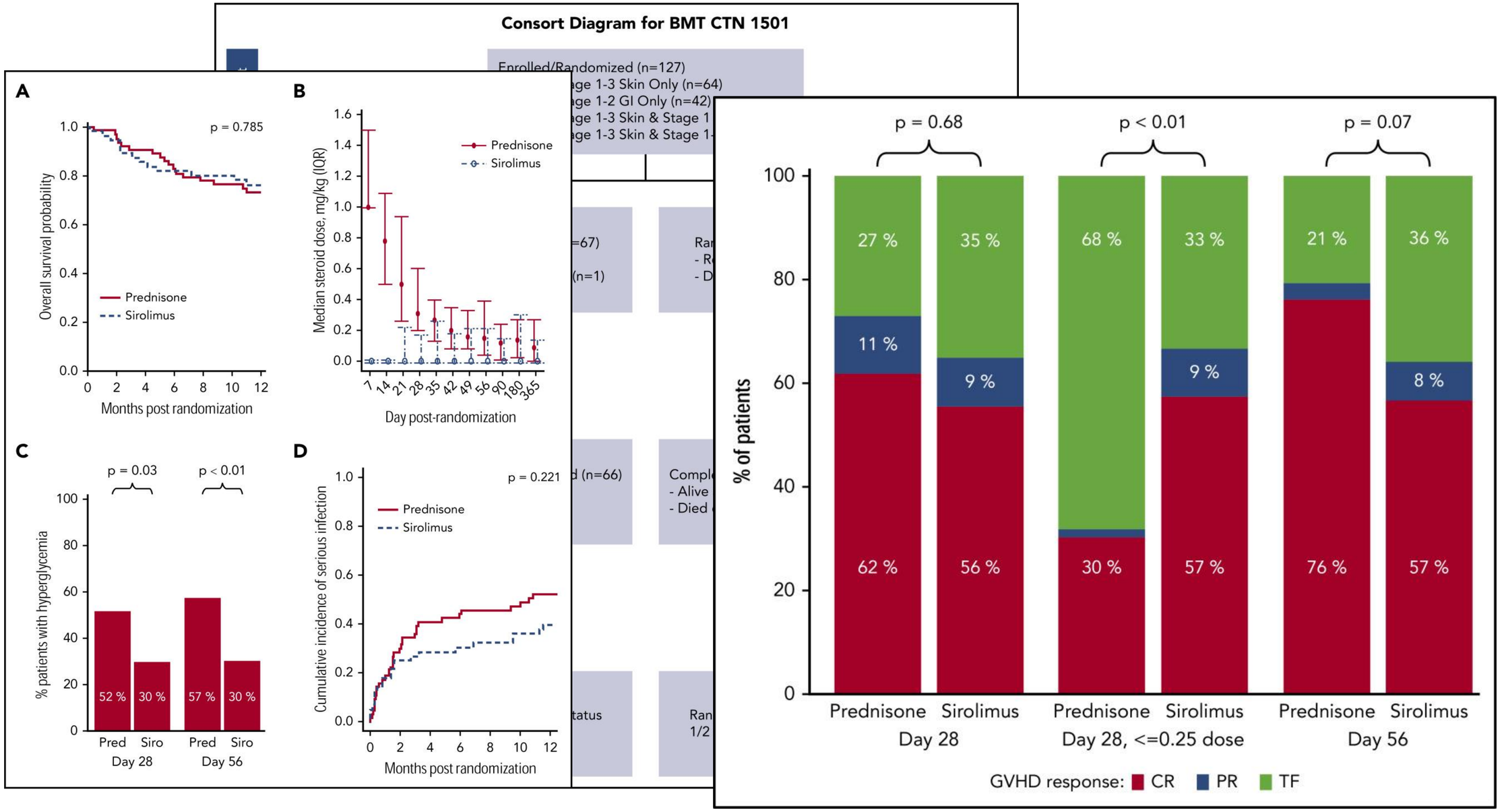




Mohty. EBMT 2021. Abstr O067.

Slide credit: clinicaloptions.com

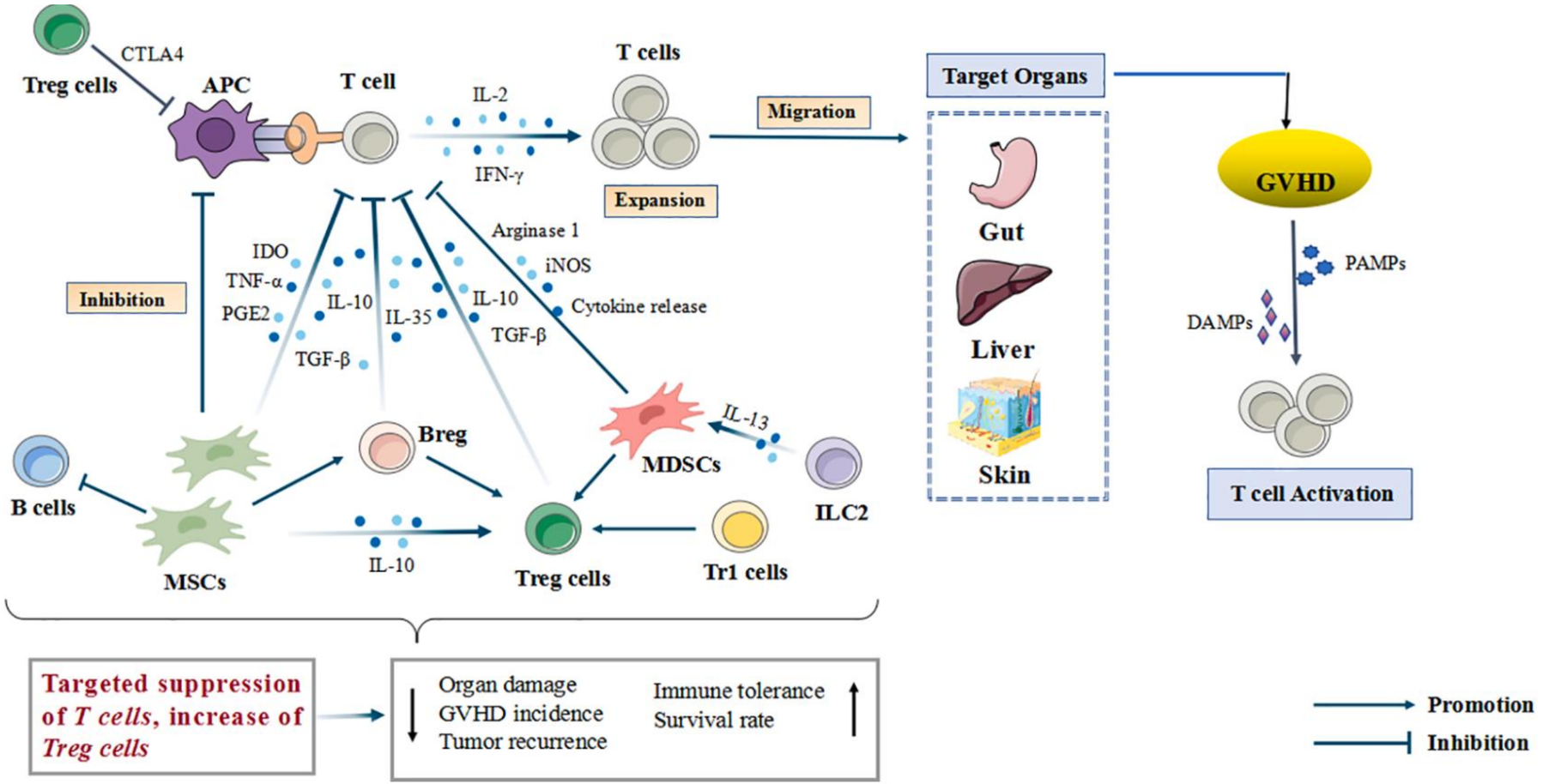
Sirolimus – BMT CTN 1501



2nd Line treatments

Investigational agent	Study design	Patients, *N*/years	Overall response rate	Complete response rate	Overall survival rate	Main toxicities	References
Pentostatin	Phase I	23(22 assessable for response)/0–63	77%	64%	26%, median survival 85 days	Lymphopenia: 100% Thrombocytopenia: 4% Infection: 9%	Bolaños-Meade et al. (125)
	Phase II	62/1–53	90%	68,8%	54.6% at 4 years	CMV reactivation: 39% Infections as cause of death: 11%	Bordigoni et al. (119)
	Retrospective	57/0–57	54%	76% for patients ≤18 years old	Median survival: 3.6 months	Opportunistic infection: 95% Bacterial infection: 88% Fungal infection: 51% Viral infection: 53% CMV: 35% EBV: 7%	Perales et al. (120)
Anti IL-2 receptor antibody basiliximab	Retrospective	34/2–38	82%	32%	20% at 5 years	NA	Funke et al. (121)
	Retrospective	230 (74 < 18 years)	78.7	60.9	61.7% at 4 years	Bacterial infection: 52.6% Fungal infection: 16.1% Viral infection: 3.8%	Liu et al. (122)
	Retrospective (haploidentical HSCT)	100/1–17	85%	74%	76,2% at 3 years	Bacterial infection: 11% Fungal infection: 7% CMV viremia: 53% EBV viremia: 11% HHV-6 viremia: 7%	Tang et al. (123)

MSC and MSC-Exo



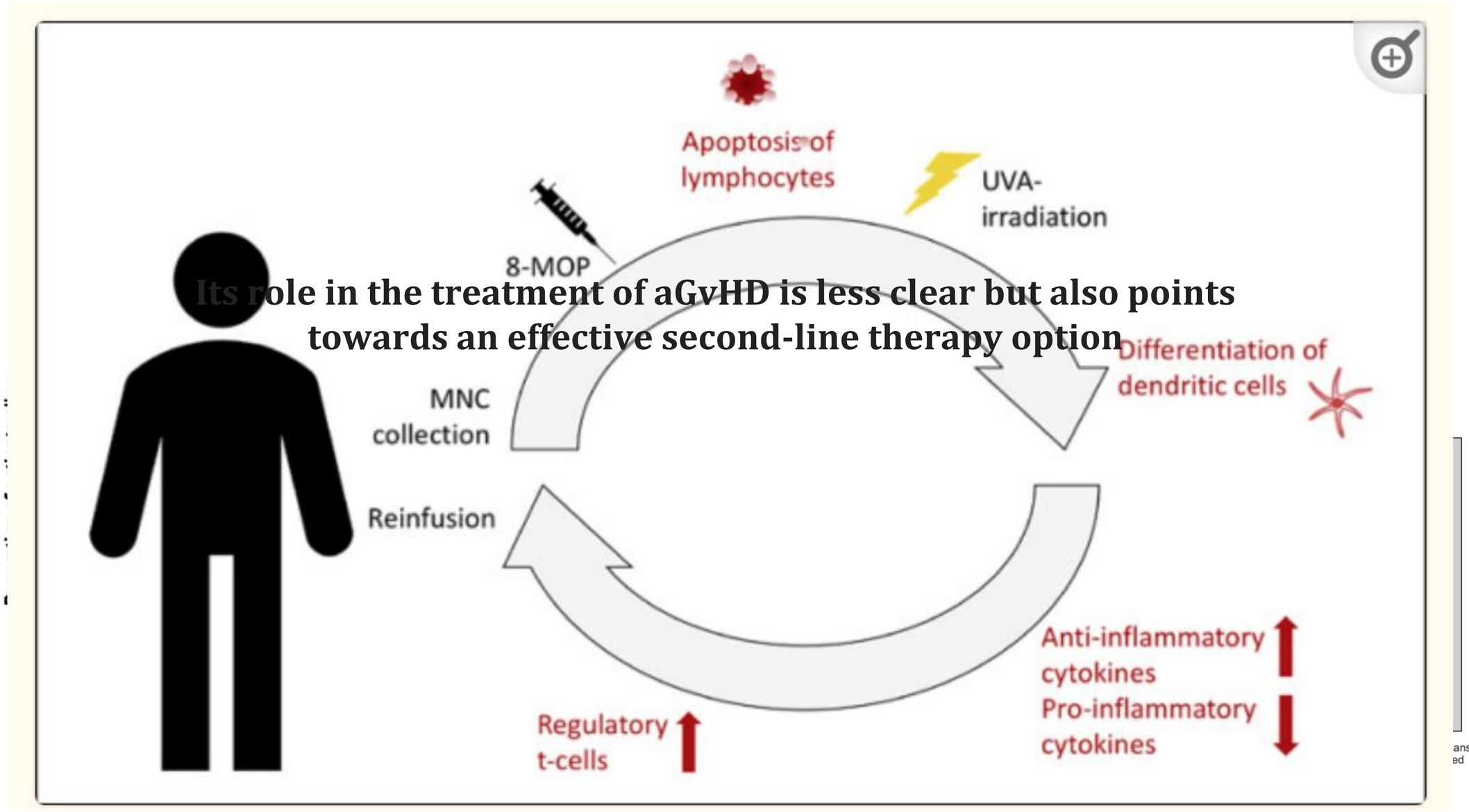
remestemcel-L

Morata-Tarifa C, et al. *Stem Cell Res Ther.* (2020) 11:64.

Bonig H et al. "MSC-FFM". *Cells.* (2019) 8:1577. doi: 10.3390/cells8121577

Kebriaei P et al. Biol Blood Marrow Transplant. (2020) 26:835–44.

Extracorporeal Photopheresis



Its role in the treatment of aGvHD is less clear but also points towards an effective second-line therapy option

Novel Approaches for GVHD

- Bendamustine
- IL-2
- Defibrotide
- Atorvastatin
- Leronlimab (CCR5)
- Tocilizumab
- CD24f
- Bortezomib
- Fecal transplant
- Vedolizumab

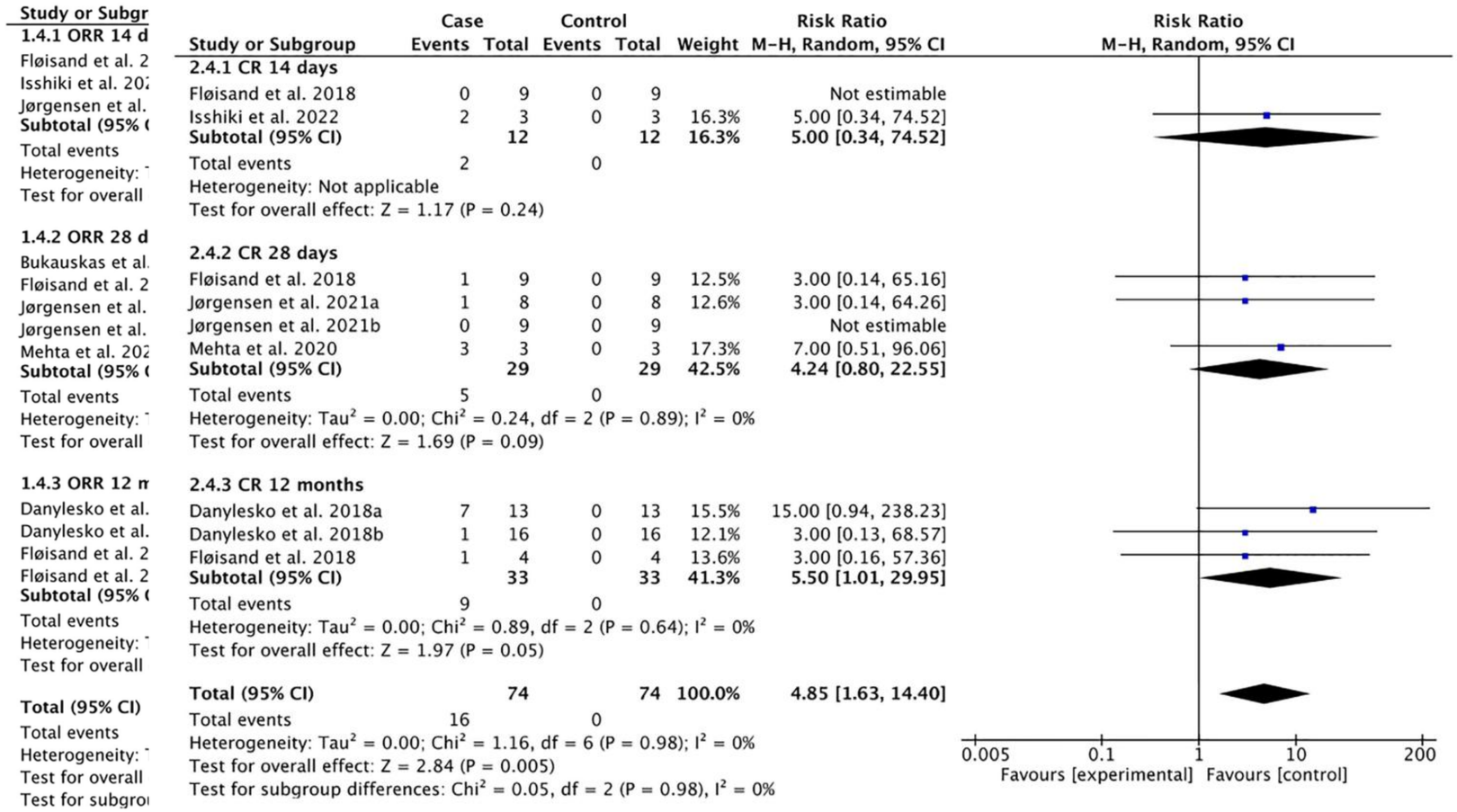
- Itacitinib
- Canabidiol
- CD40L blockade
- Tildrakizumab (anti-IL23p19)
- Expanded regulatory T-cells
- Basiliximab
- Telmisartan
- RGI 2001 (α gal-cer [CD1d ligand])
- MSC

- Panobinostat
- Carfilzomib
- Rituximab
- Milatuzumab (anti-CD74)
- Maraviroc
- Brentuximab vedotin

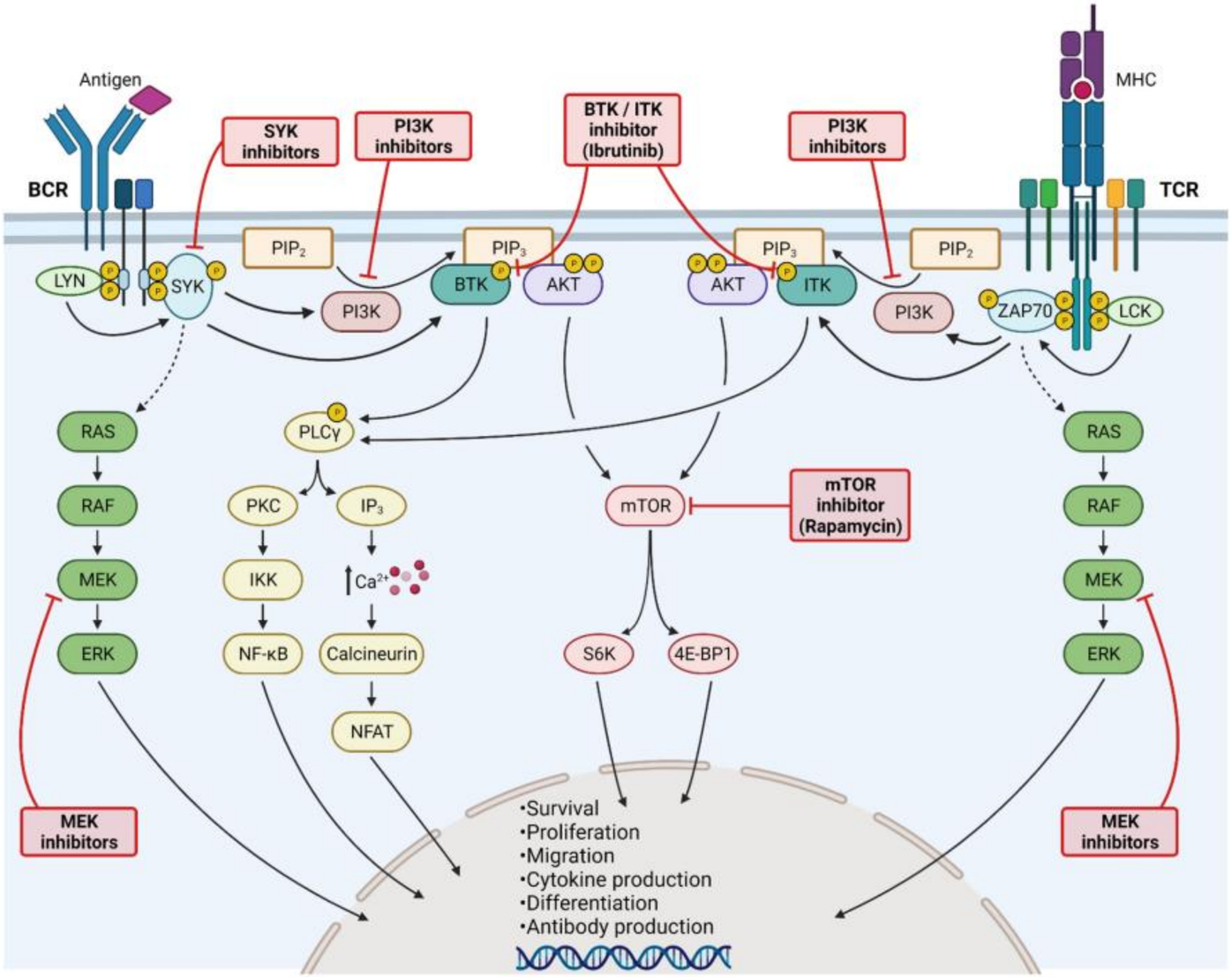
Literature Review | Article | Full-text available

Vedolizumab for acute gastrointestinal graft-versus-host disease: A systematic review and meta-analysis

November 2022 · Frontiers in Immunology 13:1025350



KIs in aGVHD treatment

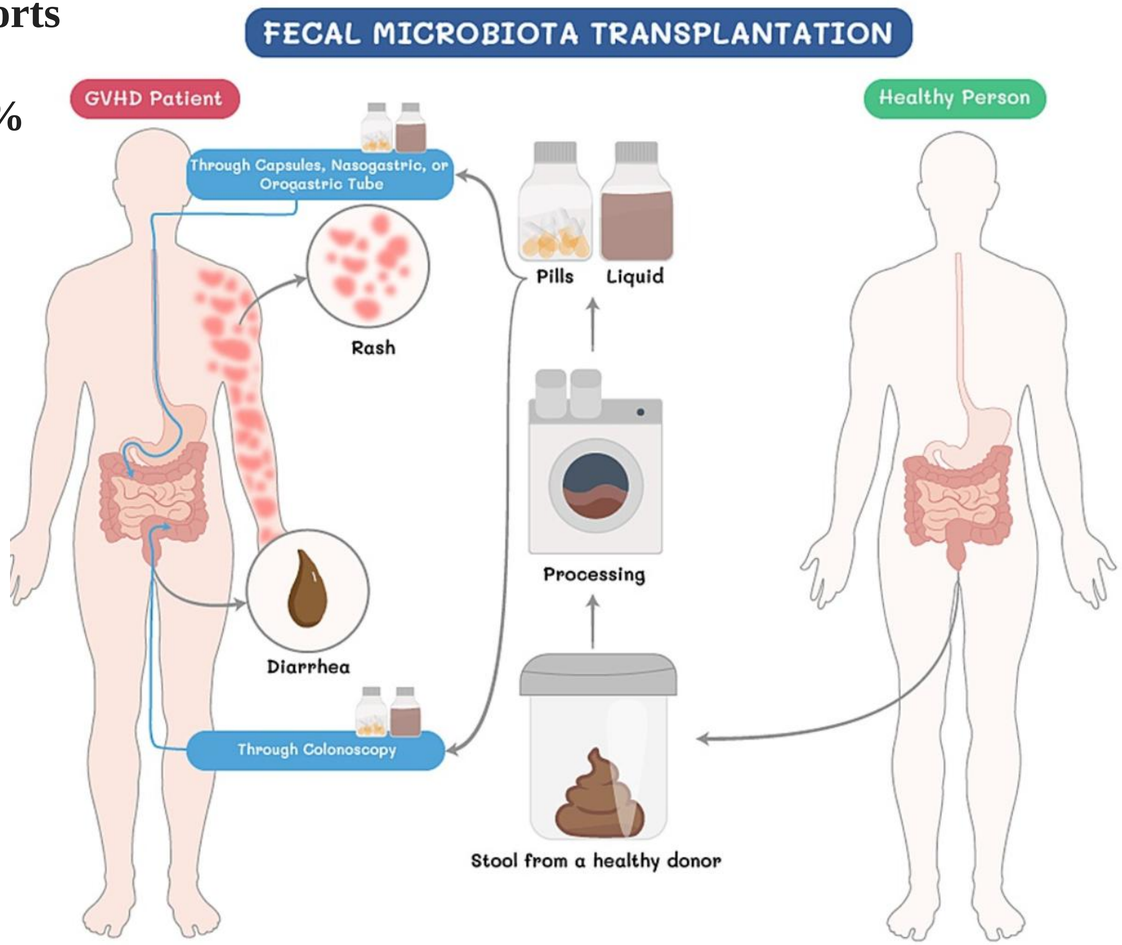


FMT in aGVHD

Restoration of the Original Inhabitants: A Systematic Review on Fecal Microbiota Transplantation for Graft-Versus-Host Disease

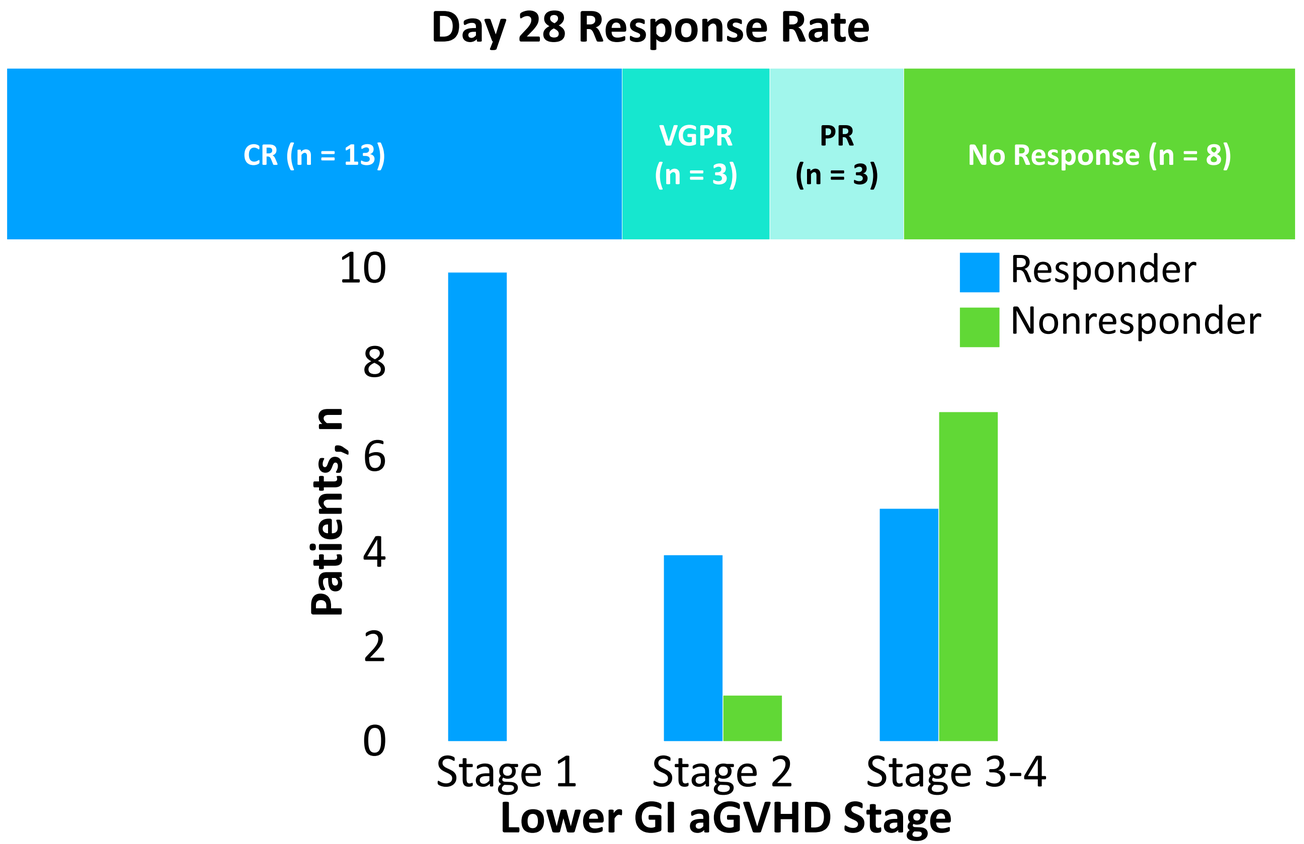
Mohamad S. Alabdaljabar [1], Hafiz M. Aslam [2], Sindhusha Veeraballi [3], Faizan A. Faizee [4], Batool H. Husain [5], Shumaila M. Iqbal [6], Shahrukh K. Hashmi [7]

- **79 patients from six studies and five case reports**
- **Complete remission (CR) occurred in 55.9%**
- **Partial remission (PR) occurred in 26.5%**
- **ORR of 82.4%**
- **Nearly no toxicity**



IL-22 “GI Protectant” With Steroids as Initial Therapy for GI GVHD

- F-652: recombinant fusion protein of human IL-22 dimer and human IgG2 Fc with an extended $t_{1/2}$
- Phase II trial with steroids[2]



1. Hanash. Immunity. 2012:37:339. 2. Ponce. TCT 2020. Abstr 68. 3. NCT04539470.

Urinary-Derived Human Chorionic Gonadotropin/ Epidermal Growth Factor for aGVHD: Study Design

- Prospective phase II trial

Patients with life-threatening aGVHD; creatinine <2.5x ULN; LVEF ≥35%

First line: Minnesota High Risk

uhCG/EGF 2000 units/m^2 SC every other day x 7 days + High-dose steroids* (n = 22)

Second line: no response to first line or GVHD flare

uhCG/EGF 2000 units/m^2 SC (steroid dependent) or 5000 units/m^2 SC (steroid refractory) every other day x 14 days + SoC immunosuppression* (n = 22)

*Responders eligible to receive optional maintenance doses twice weekly x 5 wk.

- **Primary outcome:** Day 28 response
- **Secondary outcomes:** safety, survival, exploratory metabolomics analysis, biomarkers

Holtan. ASH 2021. Abstr 261. NCT02525029.

uhCG/EGF for aGVHD: Day 28 Response (Primary Outcome) and Survival Outcomes

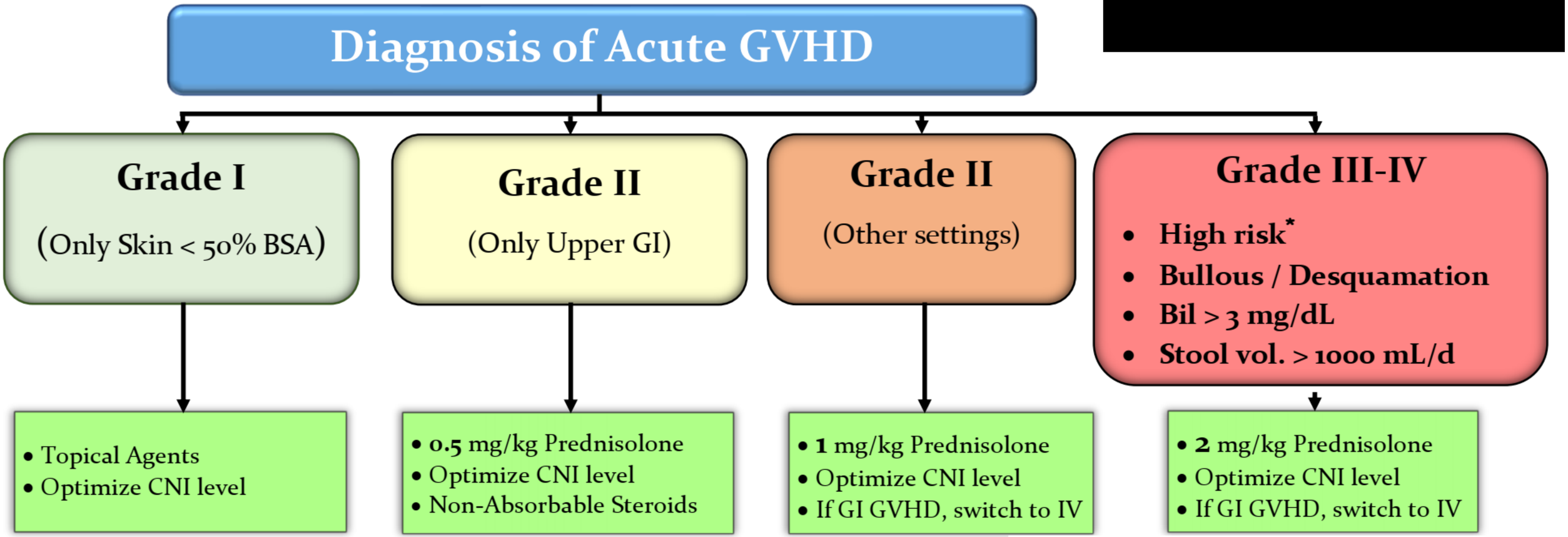
Outcome, n (%)	First-line High Risk (n = 22)	Second Line (n = 22)	All Patients (N = 44)
CR	64	50	57
PR	0	23	11

- Median OS for entire cohort: 1.2 yr
- 2-yr survival 67% vs 12% for responders vs nonresponders, respectively; *P* <.01

Holtan. ASH 2021. Abstr 261.

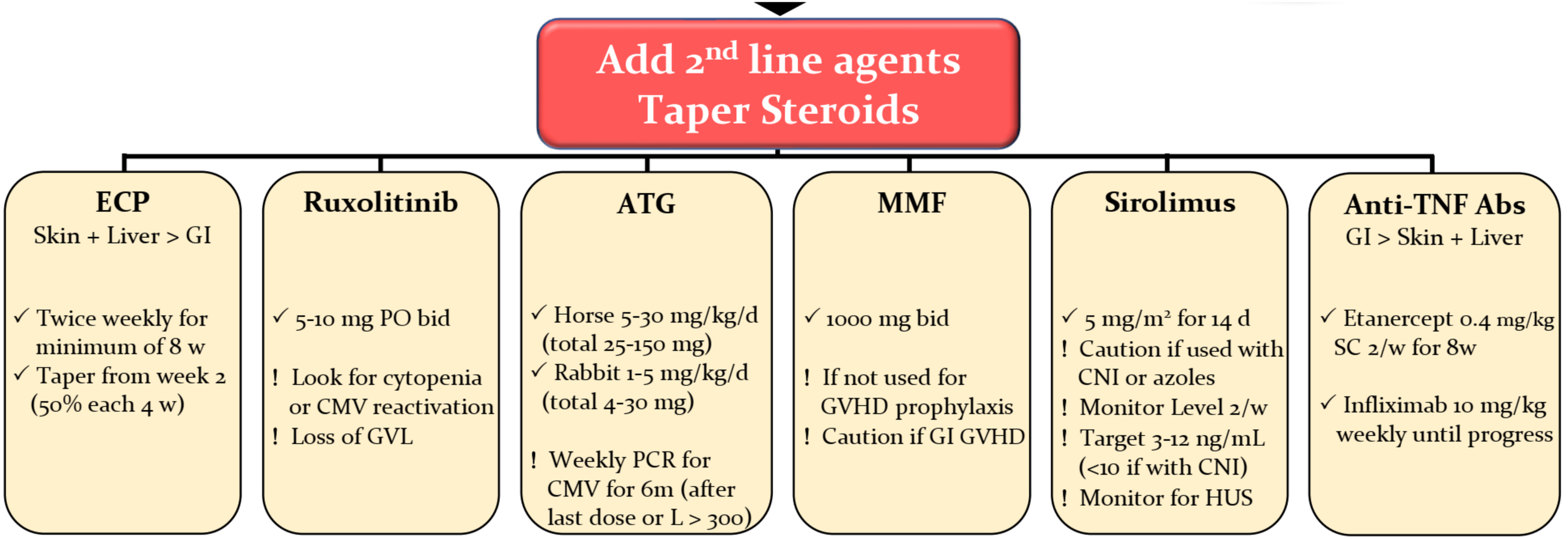
- ✓ **Centers should have and follow their institutional guidelines, and the patients should be treated in trials as far as possible**

Our Center – 1st line

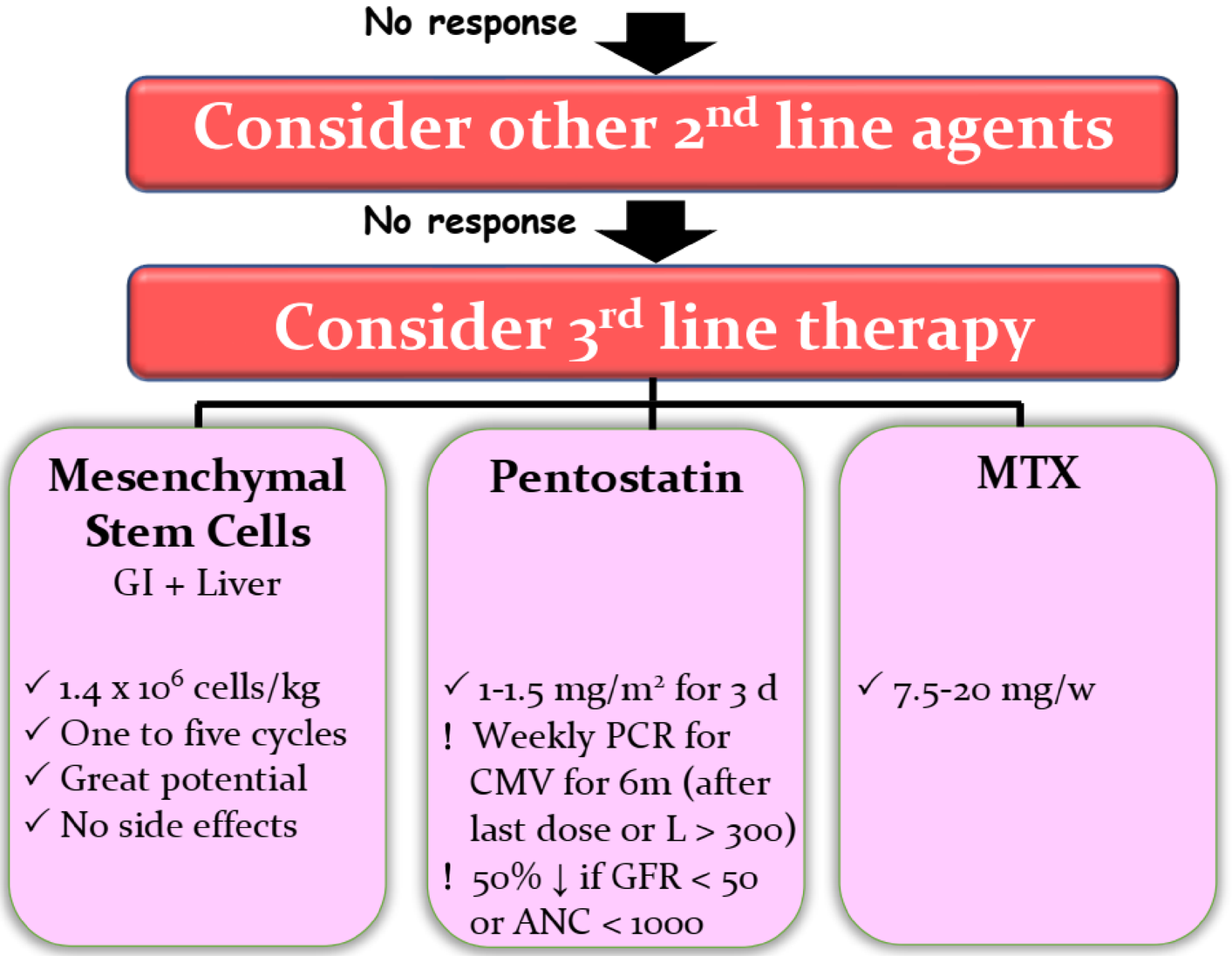


* https://redcap.ahc.umn.edu/surveys/?s=bNmFhseJIf

Our Center – 2nd line



Our Center – 3rd line



Conclusions

- 2-yr OS of patients with steroid-refractory acute GVHD is below 40%
- Ruxolitinib was approved by the FDA for SR-aGVHD in 2020
- Novel regenerative approaches such as IL-22 and GLP-2 treatment in addition to immunosuppression may help improve the outcome of patients with SR-aGVHD
- New targets and new targted therapy

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Extracorporeal Photopheresis (ECP)

Saeed Mohammadi
PhD in Hematology and Transfusion Medicine
Fellowship of Clinical Laboratory Sciences (FCLS)
Associate Professor at Research Institute for Oncology, Hematology and Cell Therapy

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

Extra corporeal photochemotherapy in steroid refractory graft versus host disease: A review of guidelines and recommendations

Saeed Mohammadi[a], Ashraf Malek Mohammadi[a], Amir Hossein Norooznezhad[a], Kamran Alimoghaddam[a], Ardeshir Ghavamzadeh[a]

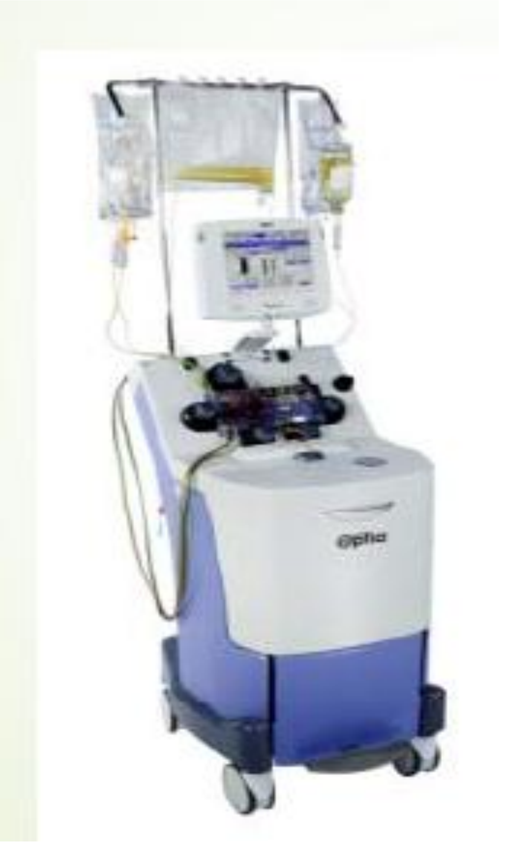
[a] *Hematology, Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran*

What is ECP

- Cell therapy
- Consists on 3 steps :
  - MNC collection
  - Transformation
    - Addition of 8-MOP
    - UVA irradiation
  - Re injection

1st step : MNC collection

- As a Stem cell collection
- 1-3 Hours
- The Patient looks at a film on laptop or listen the music
- Full automatic procedure
  - Optia (Terumo)
  - Comtec (Fresenius)
  - Amicus (Fresenius)



2nd Step : Exposure of MNC to UVA/8-MOP (transformation) - 1

15 to 30 minutes

- Transfer of MNC to special bag
- Addition of 8-MOP
- Irradiation by the UVA light

5 Technical Aspects

After Apheresis:

❖ Approximately **2TPBV**

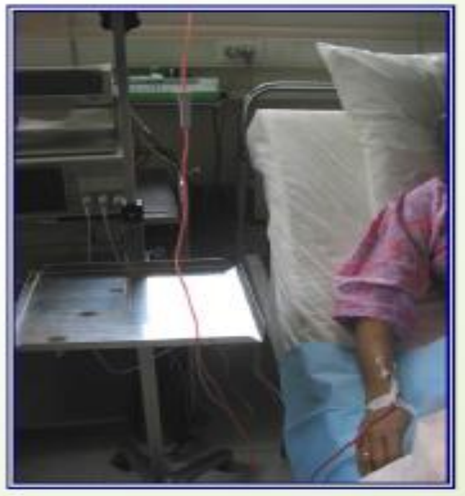
❖ The product should be treated with 8-MOP diluted to a final concentration :

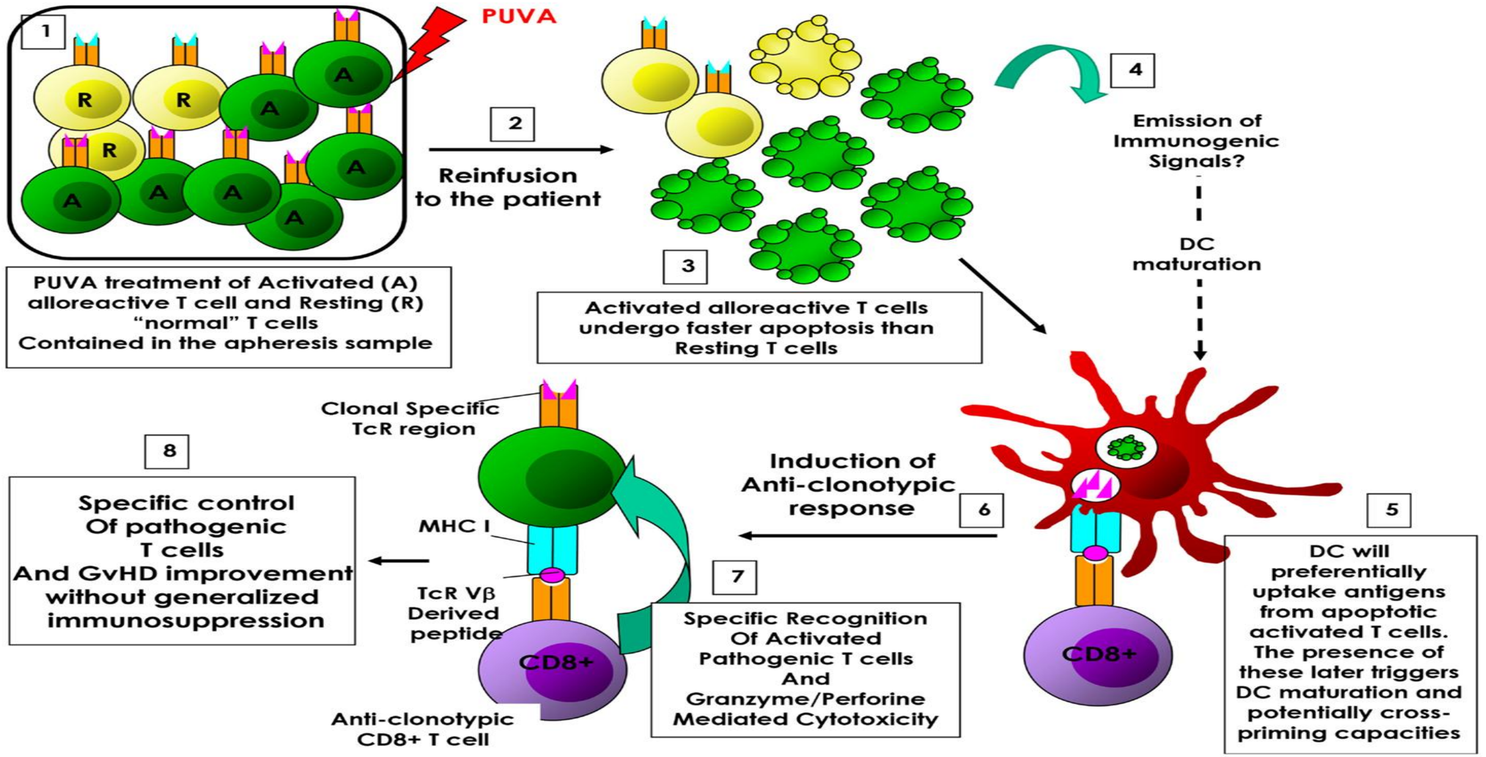
Pediatric :

- In-line technologies **34 mg/100 mL**
- Off-line technologies **20 mg/100 mL**

3rd Step : Reinjection

- As an autotransfusion
- 15 to 30 minutes





Published in final edited form as:
Curr Opin Organ Transplant. 2009 August ; 14(4): 338–343. doi:10.1097/MOT.0b013e32832ce943.

Extracorporeal photopheresis-induced immune tolerance: a focus on modulation of antigen-presenting cells and induction of regulatory T cells by apoptotic cells

Chang-Qing Xia[a], **Kim A. Campbell**[b], and **Michael J. Clare-Salzler**[a]
[a] Department of Pathology, Immunology and Laboratory Medicine, University of Florida College of Medicine, 1 Gainesville, Florida
[b] Scientific Affairs, Therakos, Inc. 437 Creamery Way, Exton, Pennsylvania, USA

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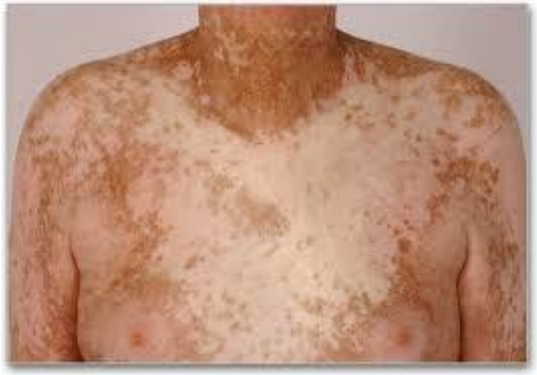
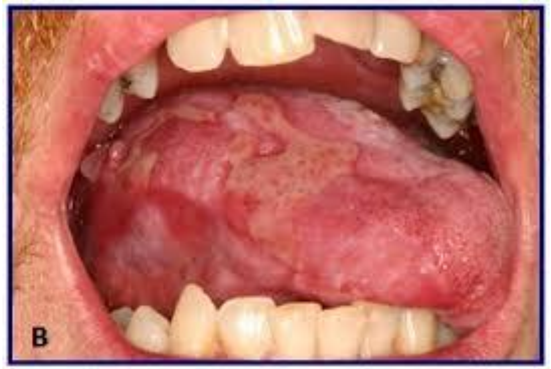
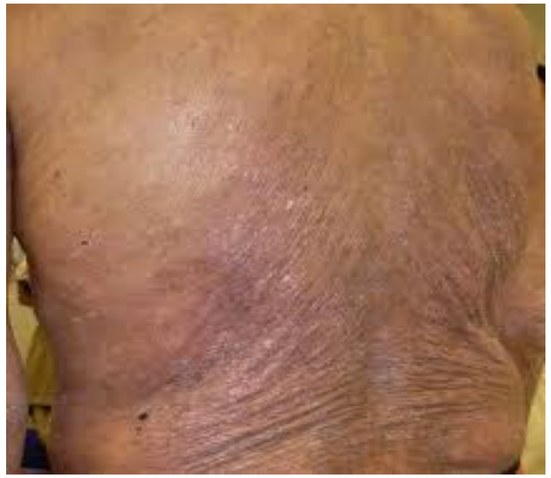
Graft-Versus-Leukemia effect seems
not to be impaired by ECP

Inclusion criteria



- ECP was strongly recommended as **second-line therapy**(grade 1b) for :
  - Skin
  - Oral
  - liver

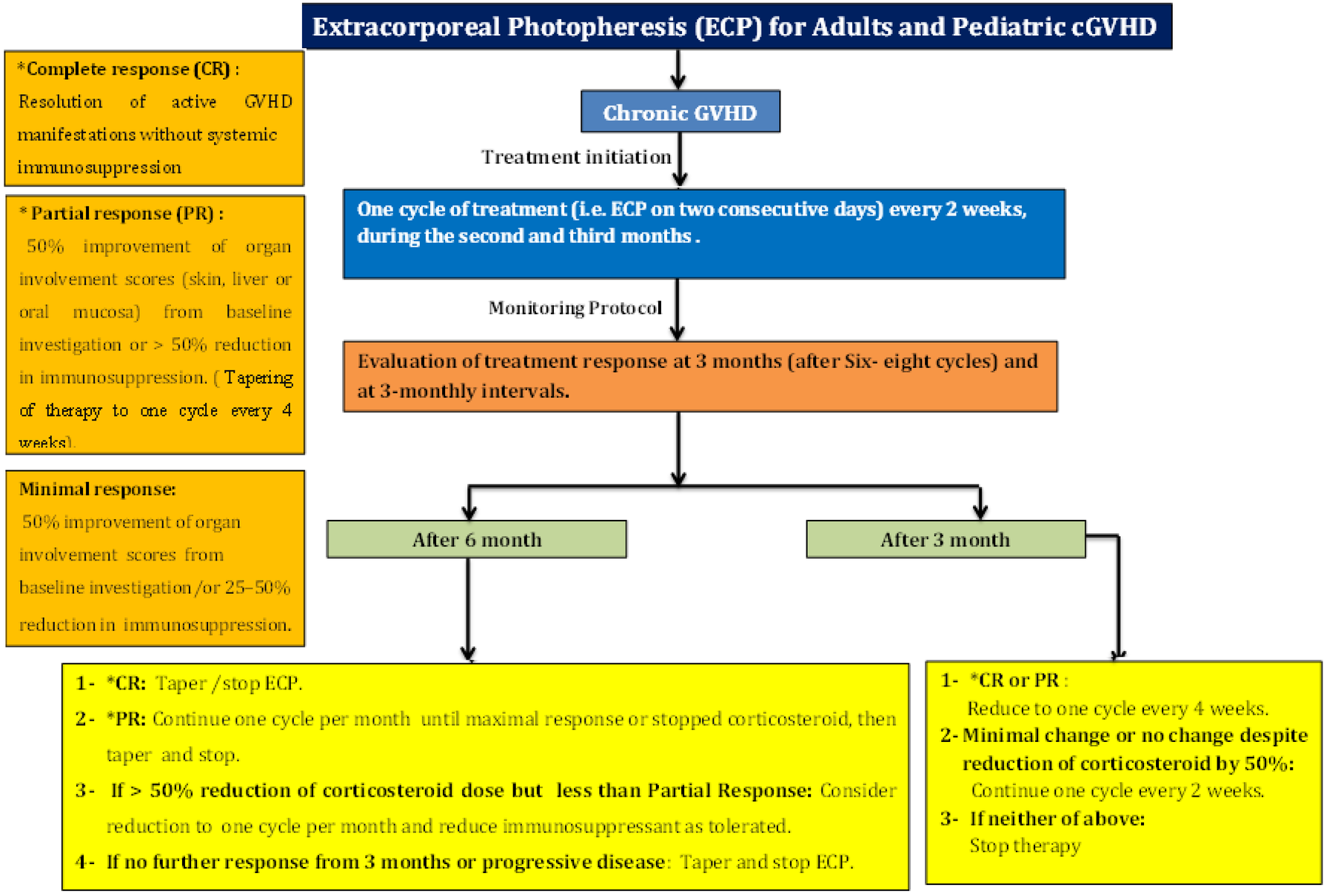




- As a **third-line treatment**(grade 2C**) :**
  - Other organs involving

- The median (range) interval between HSCT and ECP **start was 193 days.**

Extracorporeal Photopheresis (ECP) for Adults and Pediatric cGVHD

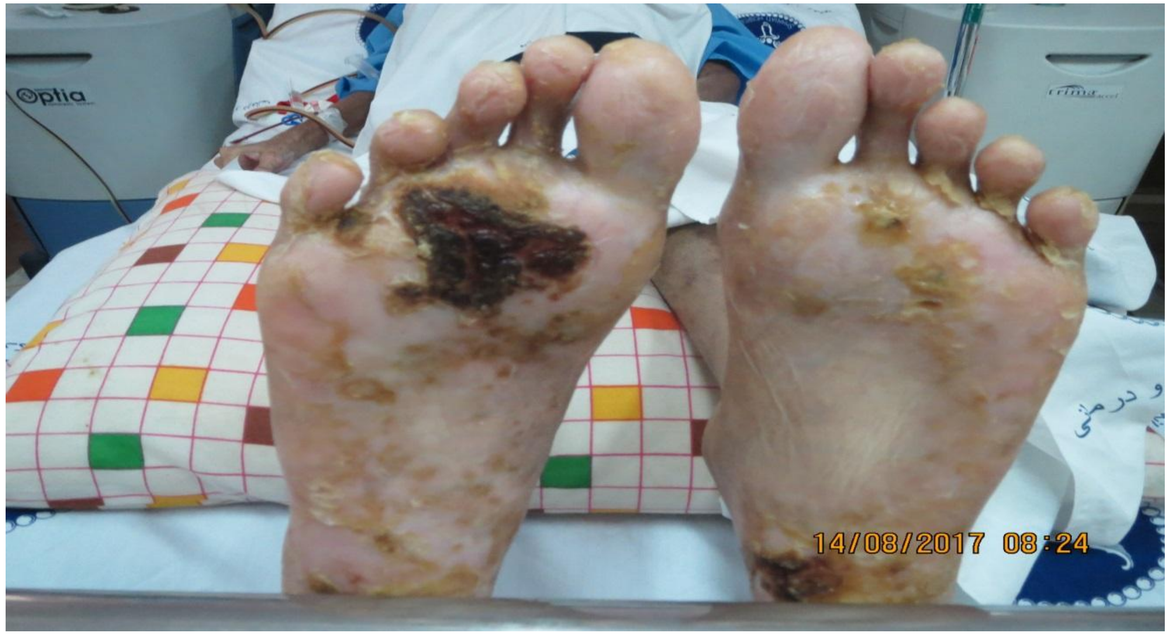


Baseline assessment

Medical historyand clinical examination to assess cGVHD symptoms /signs.
Drug history:corticosteroid dose and other cGVHD treatment.
Skin assessment: skin score, pruritus score if indicated (0–10 visual analogue scale score), +/- clinical photography.
Mouth scoresif oral disease.
Joint assessment: Karnovsky's scale (0–100), +/- physiotherapy assessment if indicated.
Eye assessment: Schirmer's test if eye involvement, +/-ophthalmology assessment.
Respiratory assessment: pulmonary function tests if lung disease (FEV1 and DLCO), +/-respiratory assessment.
Liver assessment: bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase.
Gastrointestinal assessment: frequency of stools per day, weight, gastrointestinal endoscopy if indicated.
Hematology assessment: hemoglobin, white cell count, eosinophil count, platelets
Quality of life assessment: Skindex-29 if skin involvement, EORTC 30, FACT-BMT At each visit for extracorporeal photopheresis treatment.
Biochemistry: urea and electrolytes, liver function tests.
Hematology: full blood count

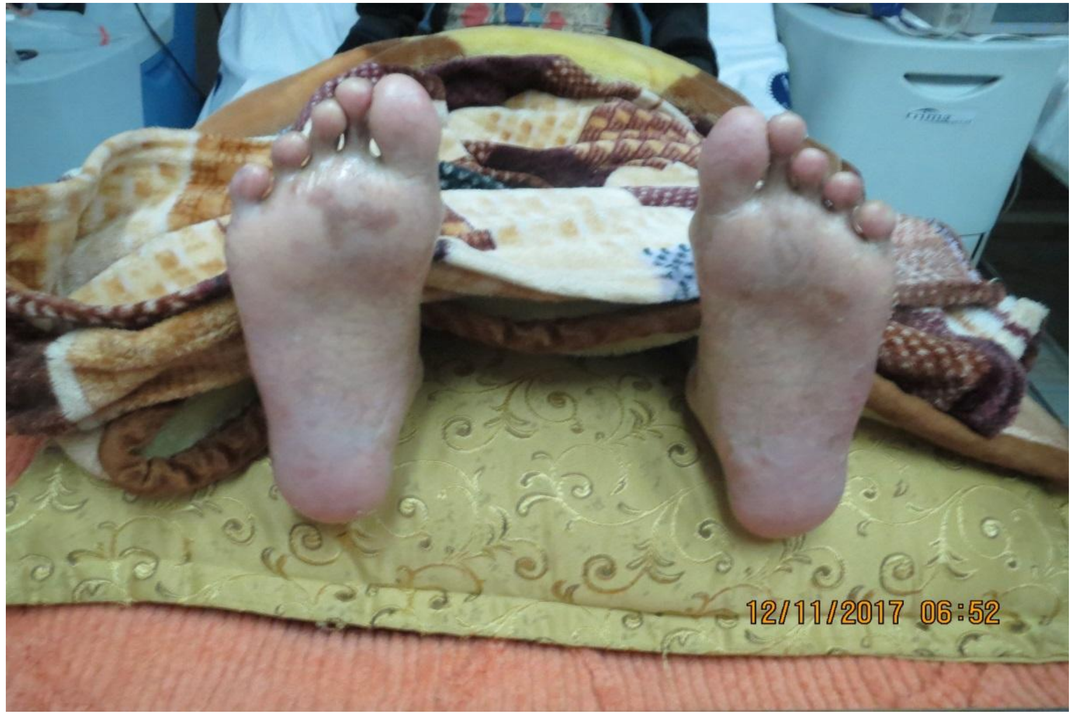
- Should be measured in **skin, oral mucosa and liver** where these organs are affected with cGVHD.

- The overall response should reflect the **most severely affected organ** but poor responses on other organs may also be considered.



Before

After



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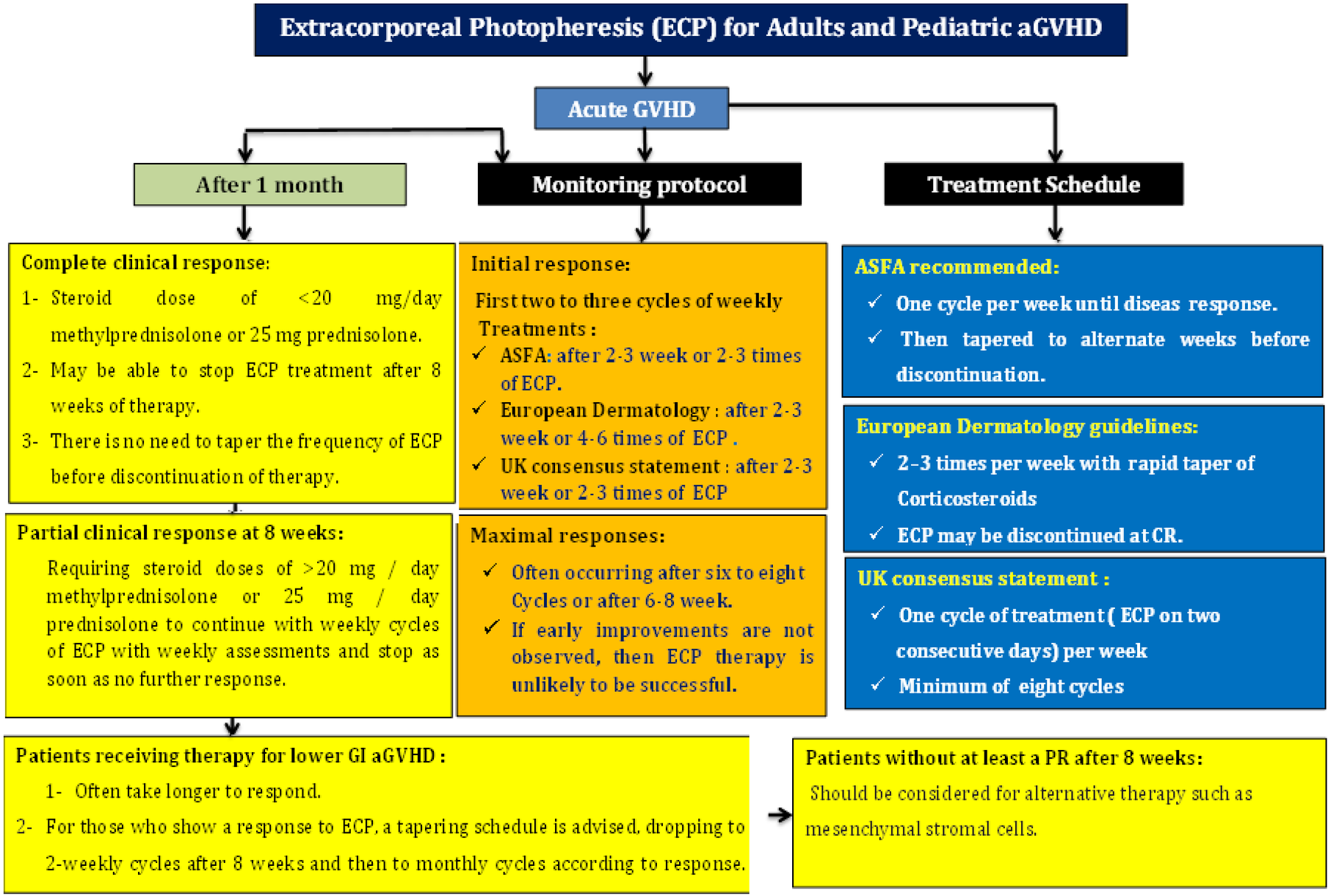
ECP in aGVHD

❖ Second-line therapy should be considered :

- **Progressive aGVHD :** after 3 days
- **Un-improving grade III/IV aGVHD**: after 1 week of persistent
- **Persistent un-improving grade II aGVHD** : after 2 weeks

❖ British Society of Blood and Marrow Transplantation:

- **After 5 days** of first-line therapy
- **After 3 days** in those with progressive disease.


Extracorporeal Photopheresis (ECP) for Adults and Pediatric aGVHD
Acute GVHD
After 1 month
Monitoring protocol
Treatment Schedule
Complete clinical response:
1- Steroid dose of <20 mg/day methylprednisolone or 25 mg prednisolone.
2- May be able to stop ECP treatment after 8 weeks of therapy.
3- There is no need to taper the frequency of ECP before discontinuation of therapy.
Initial response:
First two to three cycles of weekly Treatments :
✓ ASFA: after 2-3 week or 2-3 times of ECP.
✓ European Dermatology : after 2-3 week or 4-6 times of ECP .
✓ UK consensus statement : after 2-3 week or 2-3 times of ECP
ASFA recommended:
✓ One cycle per week until diseas response.
✓ Then tapered to alternate weeks before discontinuation.
European Dermatology guidelines:
✓ 2–3 times per week with rapid taper of Corticosteroids
✓ ECP may be discontinued at CR.
UK consensus statement :
✓ One cycle of treatment (ECP on two consecutive days) per week
✓ Minimum of eight cycles
Partial clinical response at 8 weeks:
Requiring steroid doses of >20 mg / day methylprednisolone or 25 mg / day prednisolone to continue with weekly cycles of ECP with weekly assessments and stop as soon as no further response.
Maximal responses:
✓ Often occurring after six to eight Cycles or after 6-8 week.
✓ If early improvements are not observed, then ECP therapy is unlikely to be successful.
Patients receiving therapy for lower GI aGVHD :
1- Often take longer to respond.
2- For those who show a response to ECP, a tapering schedule is advised, dropping to 2-weekly cycles after 8 weeks and then to monthly cycles according to response.
Patients without at least a PR after 8 weeks:
Should be considered for alternative therapy such as mesenchymal stromal cells.

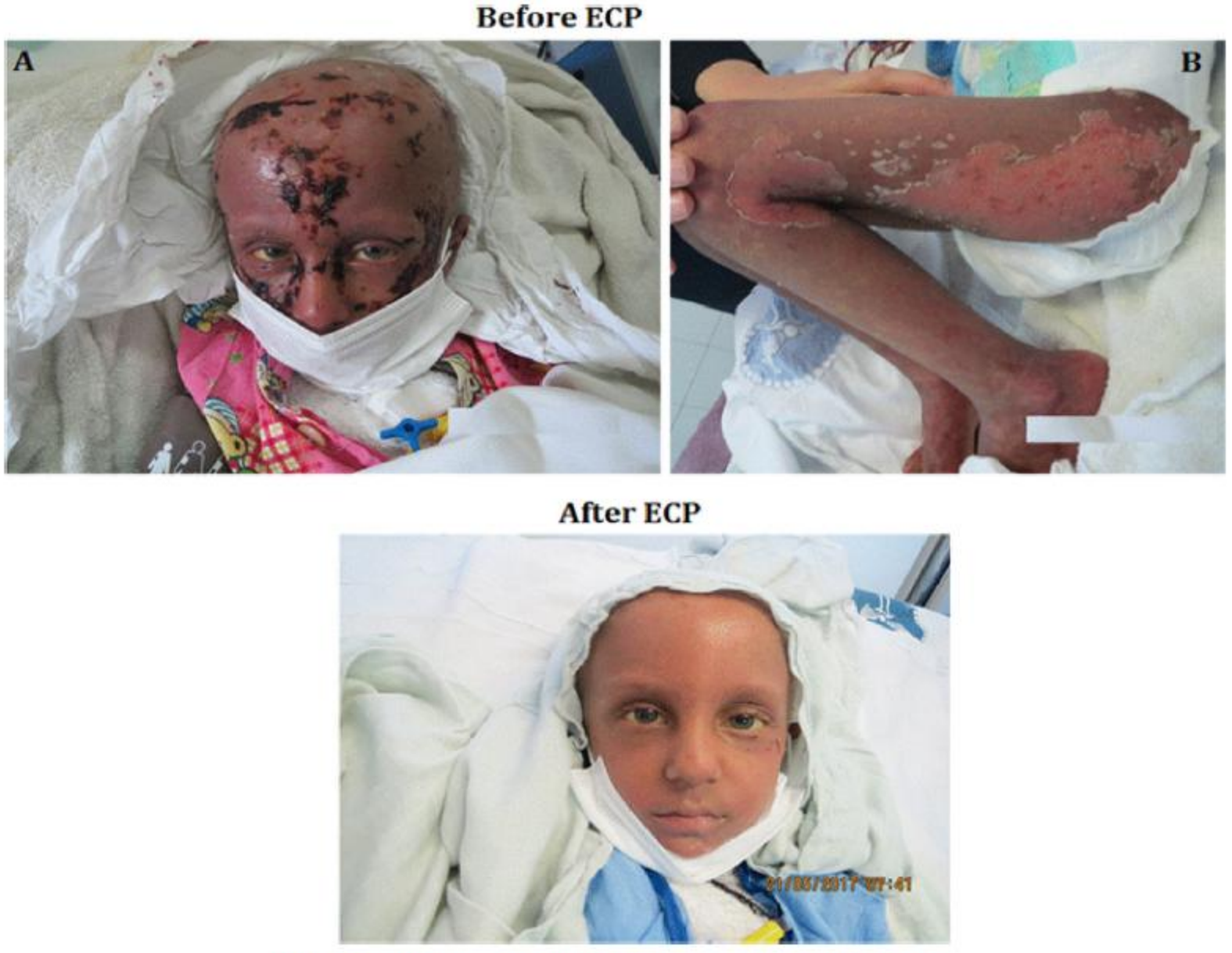


Fig. 1. Differences between skin manifestations of aGVHD before and after ECP.

Product	Identifier	Cell therapy	n
MSC	NCT02359929	Autologous BM-derived MSC for the treatment of acute and chronic GVHD	24
	NCT02032446	Umbilical cord derived MSC in combination with pentostatin for steroid-refractory acute GVHD	47
	NCT03847844	Umbilical cord derived MSC for steroid-refractory acute GVHD	40
Treg	NCT02423915	Fucosylated Treg at day −1 pre-HCT to prevent GVHD	47
	NCT01795573	Donor Treg cells at day −2 pre-HCT to prevent GVHD	48
	NCT02749084	Donor Treg to treat refractory chronic GVHD	20
	NCT02385019	Donor Treg to treat refractory chronic GVHD	22
	NCT03683498	Donor Treg to treat ruxolitinib-refractory chronic GVHD	16
	NCT01903473	Donor Treg in combination with rapamycin to treat ruxolitinib-refractory chronic GVHD	35

Search terms: "graft versus host disease" and "MSC," "Treg," "ILC," "dendritic cells," "iNKT cells," MDSC," "CAR T cells," and "CHAR T cells." The latter 6 search terms did not yield any active studies.

BM, bone marrow; n, expected number of patients to be included in the trial.

Several questions must be answered in the coming years to improve outcomes

- Can biomarkers be used repeatedly over weeks to months as a guide to tapering immunosuppression?
- Which patients need different modes of supportive care (eg, remediation of dysbiosis vs tissue damage), and can this even be distinguished biologically?
- How long should adjunct repair- based therapies such as uhCG/EGF be continued to achieve maximal mucosal healing?
- What other targets of aGVHD (eg, the endothelium) should be treated?
- Additional clinical trials are urgently needed to address these questions.
- What do perform standardizing data reporting
- Question: over suppression of aGVHD may be facilitate cGVHD??Relapse/Graft Failure

- 1-valid and reliable tool specific for symptoms of acute GVHD;
- (2) the need for frequent patient -reported assess-ments, which can place substantial burden on this acutely ill population; and
- (3) lack of robust studies correlating the objec-tive response criteria with clinically meaningful changes in QOL and acute GVHD symptoms
- clinicians should at minimum screen for psychological distress.
- serial patient -reported outcomes monitoring during the acute GVHD course will help clinicians guide clinical care in addressing the unmet needs of this popula-tion, as well as monitor potential response to therapy

Cyclosporine & Tacrolimus Nephrotoxicity

Bita Shahrami

PharmD, iBCPS, Fellowship of Critical Care Pharmacotherapy

Assistant Professor at Tehran University of Medical Sciences

CNI nephrotoxicity

- The most common adverse effects
- Occurs to some degree in all patients!

- Most data on CNI nephrotoxicity pertain to Cyclosporine since it has been used for a much longer time.
- However, a similar pattern of kidney injury from cyclosporine is seen with the use of Tacrolimus, thereby suggesting a drug class effect.

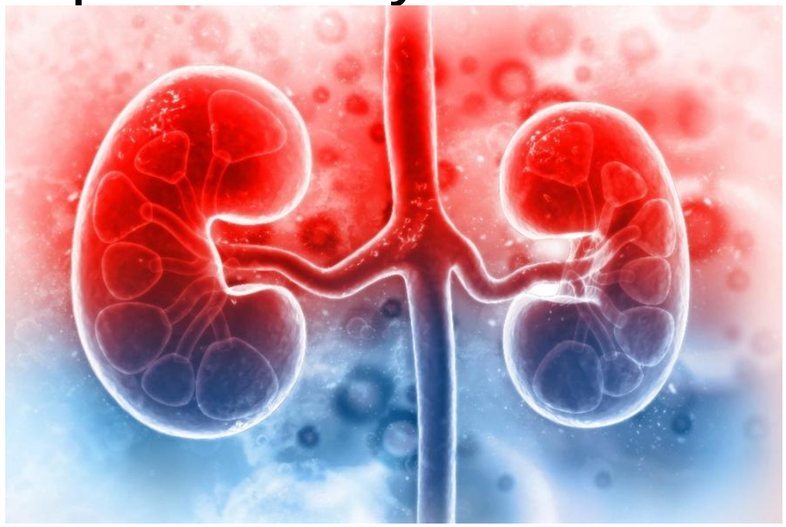
CNIs ADR?!

- It is important to distinguish CNIs-associated nephrotoxicity from ARDs of other drugs:
  - MTX
  - Cyclophosphamide
  - Amphotericin B
  - Vancomycin
  - Aminoglycosides
  - GVHD

Forms of CNI nephrotoxicity

1. Functional or acute renal dysfunction

2. Structural or chronic nephrotoxicity



Structural or chronic nephrotoxicity

- Usually seen after 6 months of therapy
- Associated with proteinuria and tubular dysfunction
- May be irreversible
- Chronic progressive deterioration in kidney function
- May present with hyperkalemia, hypomagnesemia, hyperchloremic metabolic acidosis, hyperuricemia, and HTN

Electrolyte and acid-base disturbances

- CNIs have also been associated with a number of electrolyte and acid-base abnormalities that are a result of CNI-induced tubular dysfunction.
  - Hyperkalemia
  - Hyperuricemia and gout
  - Metabolic acidosis
  - Hypophosphatemia
  - Hypomagnesemia
  - Hypercalciuria

CsA vs Tac

- CsA is tought to have higher nephrotoxicity potential as compared to Tac

- However, not all studies have observed this pattern!

Risk factors

- ✓ High doses of CsA or Tac
- ✓ Concomitant use of nephrotoxic drugs, particularly NSAIDs
- ✓ Salt depletion and diuretic use
- ✓ Inhibitors of CYP3A4/5 P-glycoprotein
- ✓ Genetic polymorphisms in the genes encoding *CYP3A4/5* and P-glycoprotein (*ABCB1*)

Drug interactions

Strong inhibitors

- Azoles (Ketoconazole, Itraconazole, Voriconazole)

CNI concentrations ?!

- CNI concentrations may be elevated,
- However, some patients may experience CNI nephrotoxicity even with levels below or within the targeted therapeutic range!
- Acute nephrotoxicity is more likely to associated with high CNI doses and levels

Prevention

- Reduced exposure to CNIs
  - TDM and dose adjustment
  - Consider drug-drug interactions

TDM of CNIs

- Trough levels are measured 12 hours after a dose

Target levels

- CsA

  200- 300 ng/mL during the first 3-4 weeks of HSCT

  100- 200 ng/mL if there is no GVHD after 3-4 weeks

  200- 400 ng/mL in aplastic anemia

- Tac

  10-20 ng/mL for HSCT

  14- 15 ng/mL during the first 2 weeks of HSCT

  8- 12 if there is no GVHD after 3-4 weeks

- Lower limit of normal in patients with preexisting CKD (eGFR <60 mL/min)

Dose calculation

$$K_{el} = \frac{Ln \dfrac{Cssmin}{T}}{T}$$

$$CL = K_{el} \times V$$

$$T_{1/2} = \frac{0.693}{K_{el}}$$

$$Cssmin = \frac{\dfrac{S \times F \times Dose}{V} \times (1 - e^{-kT})}{(1 - e^{-kt})}$$

Dose calculation

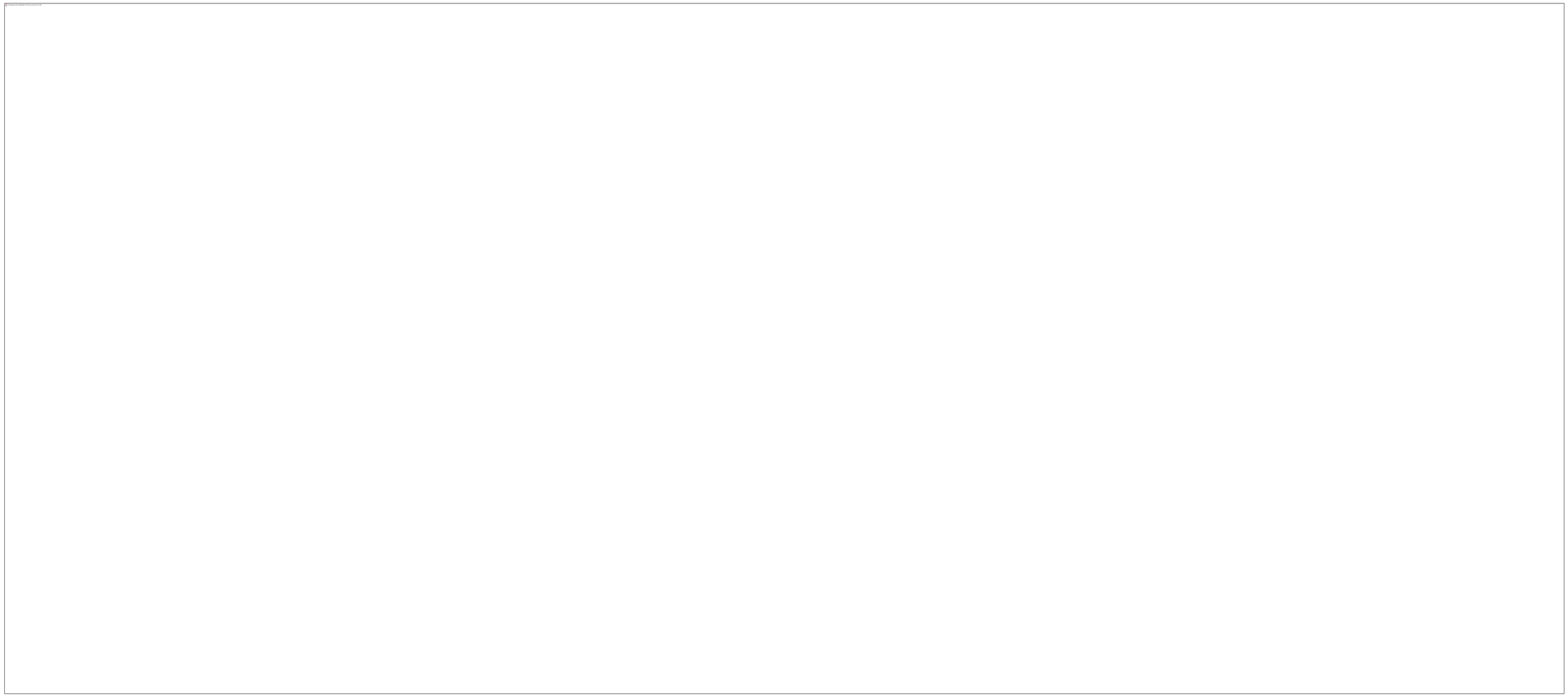
$$\text{Desired dose} = \frac{\text{Target level}}{\text{Current level}} \times \text{current dose}$$

Question

- A 32- years old man undergoing HSCT (day +20)
- A trough level of oral CsA is recorded as 150 mg/mL
- The dosing regimen is 75 mg twice daily

Which dose is appropriate for this patient?

Answer



Switching formulations

- Cyclosporine IV to oral: 1 : 3 (with comedication of azole: 1 : 1)
  - first oral dose is twice the IV dose

- Tacrolimus IV to oral: 1 : 3-5 (with comedication of azole: 50% reduction)
  - 0.03 to 0.04 mg/kg/day by continuous infusion
  - converted to the oral route (0.15 mg/kg/day, in two divided doses)

- Cyclosporine to Tacrolimus: 40 : 1

Management

- No standard treatment!
- Individualized approach is necessary!
- TDM should be applied

- If drug level is higher than target level: modify the dose
- If drug level is normal or bellow the range: reduce the dose

Expert opinion

If SrCr increases 50% above baseline: reduce dose by 25-50% and monitor SrCr for 1 month

If SrCr dose NOT decrease to 30% of baseline, further reduce dose by 25-50% for 1 month

If SrCr dose NOT decrease to 30% of baseline, discontinue CNI


REPORT
YOU
ARE
FAIL

Skin Care for Cutaneous GVHD

Dr. Bita Shahrami
PharmD, iBCPS, Fellowship of Critical Care Pharmacotherapy

General advice

Most patients report that their skin is much drier post-transplant so they should use:

✓ Emollients

- Applied regularly and liberally at least 2–3 times daily

✓ Use soap substitutes or bath additives when bathing / showering to improve hydration of the skin

Photoprotection

- Ultraviolet light exposure can trigger a flare of GVHD and can prolong or worsen cutaneous GVHD.

- UV light can also trigger phototoxic drug eruptions e.g. Voriconazole, NSAIDs.

- The risk of skin cancer is higher in patients with GVHD; this risk is already elevated by immunosuppressive agents and/or prior phototherapy treatment.

Advice should include:

- Avoiding the peak hours of sunshine (11am – 3pm)
- Using a broad spectrum sun screen SPF 30+ regularly
- Using broad-brimmed hats, long sleeves, trousers or UV-protective clothing

Physical methods of sun protection are more effective than relying on sunscreens!

اصول کلی مراقبت و سلامت پوست

- ✓ Wear cotton clothes
- ✓ Try not to get too hot or too cold
- ✓ When you are washing don’t have the water too hot
- ✓ Let your skin dry in the air or gently pat it dry instead of rubbing it
- ✓ Keep nails trimmed/filed to prevent breakage and pain
- ✓ Clear nail lacquer can be used as a nail hardener

Advise patients about self-skin examination!

- ✓ Erythematous rashes may not be symptomatic in the early stages!
- ✓ Advise patients to contact if they no
  growing lump on the skin or any sk

Topical treatments

- ✓ Moisturisers/ Emollients
- ✓ Antihistamines (for itching)
- ✓ Topical corticosteroids
- ✓ Topical tacrolimus

انتخاب پایه دارویی مناسب بر اساس محل ضایعه

As a rule:

If it’s wet, dry it; if it’s dry, wet it!

پایه	پوست صاف و بدون مو، ضایعات هایپرکراتوز	نواحی مودار	کف دست و پا	نواحی عفونی	بین انگشتان، ضایعات مرطوب و له شده
پماد	+++	-	+++	-	-
کرم	++	+	++	+	++
لوسیون	-	++	-	++	++
محلول	-	+++	-	+++	++
ژل	-	++	-	+	+
فوم	++	+++	++	++	++

+++ preferred
++ acceptable
+ infrequently used

Ointments are typically more potent than creams!

Potency of topical steroid	Examples
Mild	Hydrocortisone 1% Fluocinolone acetonide 0.01%
Moderate	Clobetasone butyrate 0.05% Fluocinolone acetonide 0.025% Triamcinolone acetonide 0.1%
Potent	Betamethasone dipropionate 0.05% Betamethasone valerate 0.1% Clobetasol propionate 0.025% Mometasone furoate 0.1% Triamcinolone acetonide 0.5% Hydrocortisone probutate
Super-potent	Betamethasone dipropionate, Augmented 0.05% Clobetasol propionate 0.05%

Topical steroids are typically used twice daily.

Low-potent topical corticosteroids

- For thinner skin areas (face, neck, axillae, and groin)
- For epidermal forms of cGVHD (ichthyosiform, lichenoid, papulosquamous)

- Hydrocortisone 1%
- Fluocinolone 0.01%
- Triamcinolone 0.1%

High-potent topical corticosteroids

- For lichen sclerosus and sclerotic forms of cGVHD.
- Especially in cases where the lesions are active or progressing
- For Poikiloderma, acral erythema

➢ Clobetasol propionate

➢ Betamethasone 0.1%

➢ Fluocinonide 0.05%

Adverse effects of topical corticosteroids

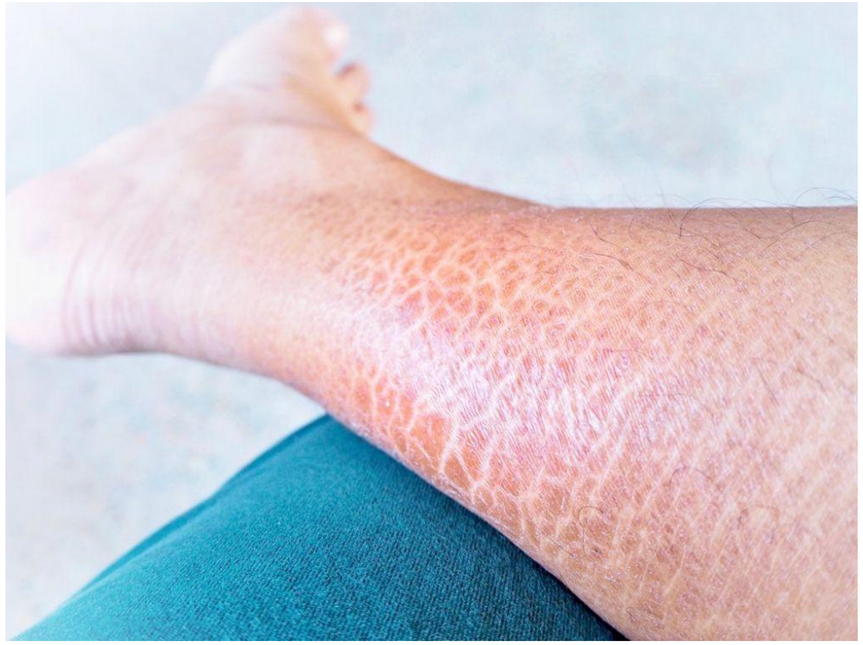
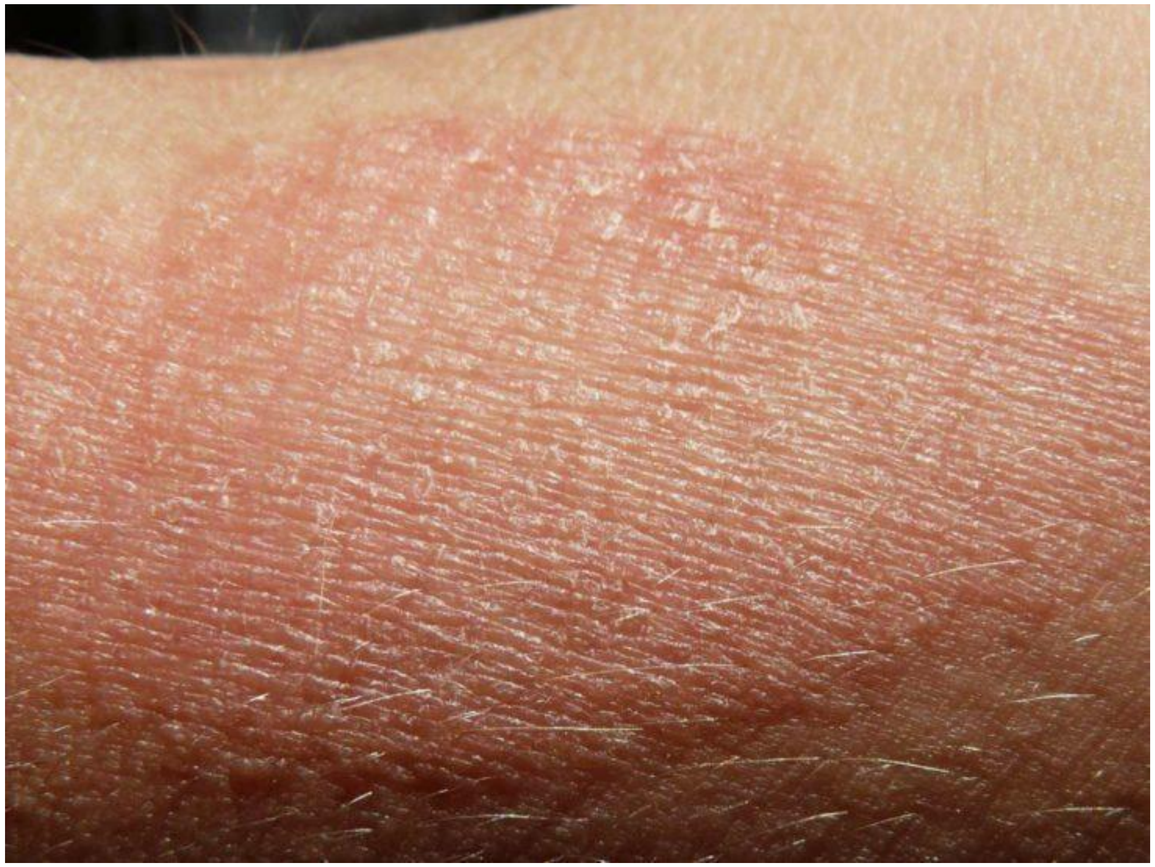
- The adverse effects associated with topical steroids include:
  - Atrophy
  - Blood vessel dilation
  - Steroid acne
  - Systemic absorption (in pro se)

Topical Tacrolimus

Topical Tacrolimus

- As a steroid-sparing agent for atopic dermatitis.
- For lichen planus-like
- In contrast to corticosteroids, tacrolimus does NOT affect collagen synthesis and can be used where atrophy is of particular concern (the face, flexural surfaces, axillae, etc.)
- Systemic absorption has been reported in patients who apply topical tacrolimus to mucosal surfaces!

Xerosis / Ichthyosis

- 
- 

Management of Xerosis / Ichthyosis

- ✓ Emollients
- ✓ C 

SP / 

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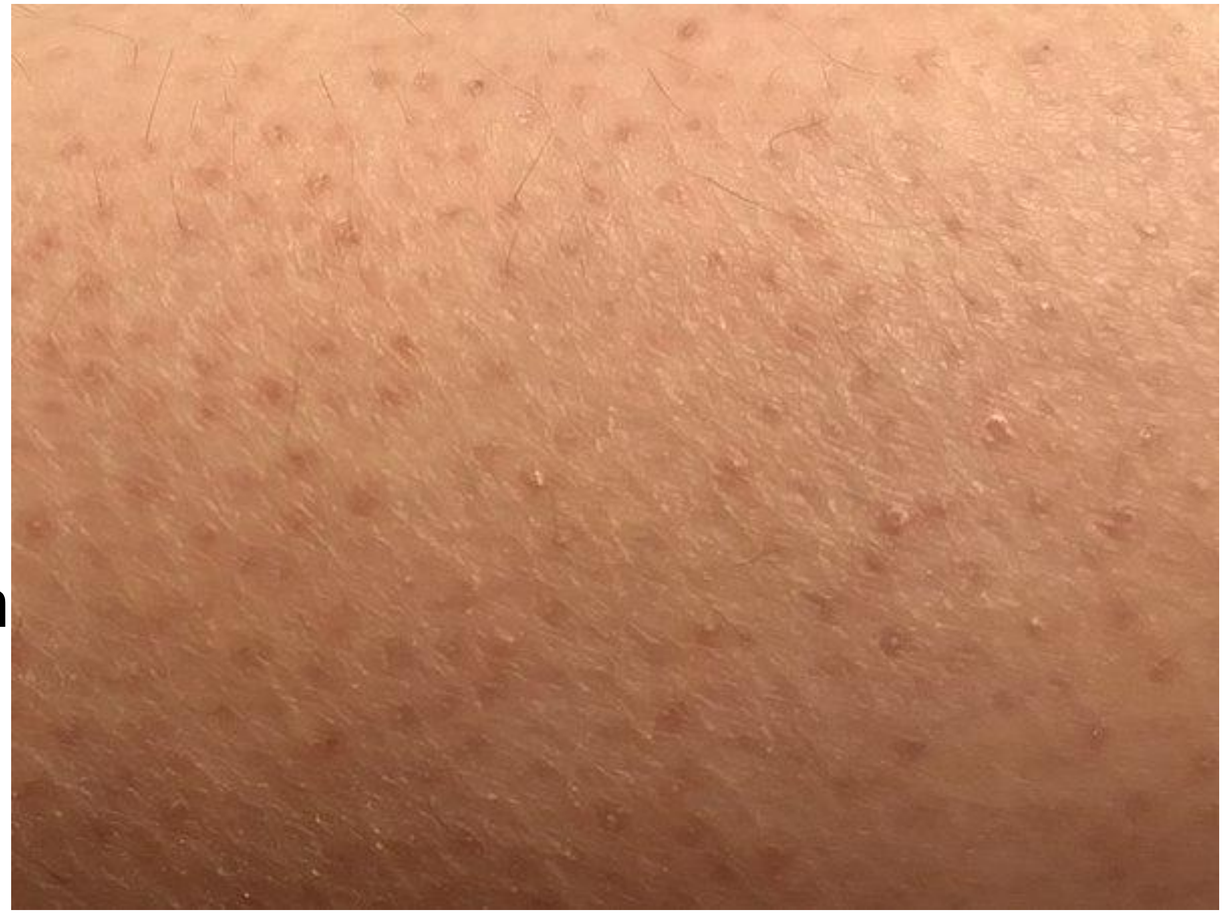
Keratosis pilaris-like

- Follicular prominence,
- Peri-follicular erythema
- ‘Hedgehog’ appearance of skin



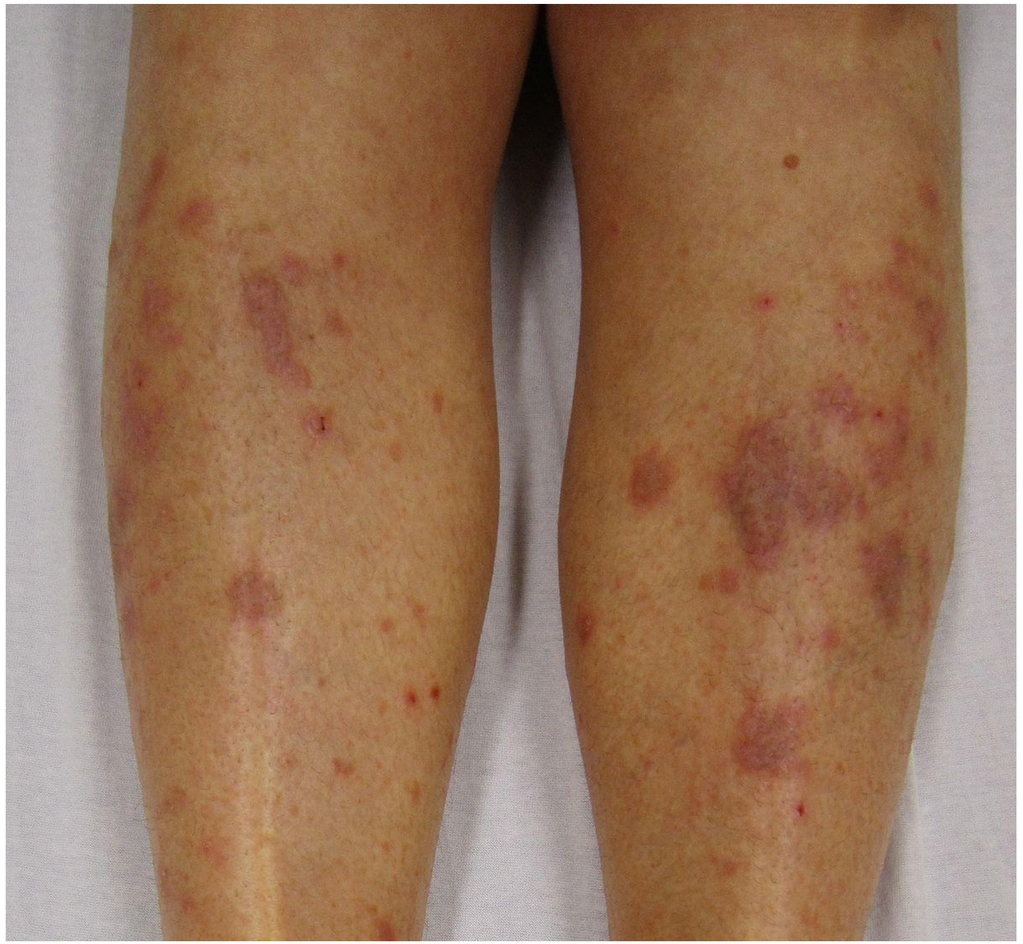
Management of Keratosis pilaris-like

- ✓ Emollients containir 

or salicylic a 

Lichen planus-like

- Purple /hyperpigmented papules
- Plaques often on extensor surfaces, acral predisposition



Management of Lichen planus-like

- ✓ Potent topical steroids
- ✓ T
- ✓ F plus UVA)

Poikiloderma

- Telangiectasia

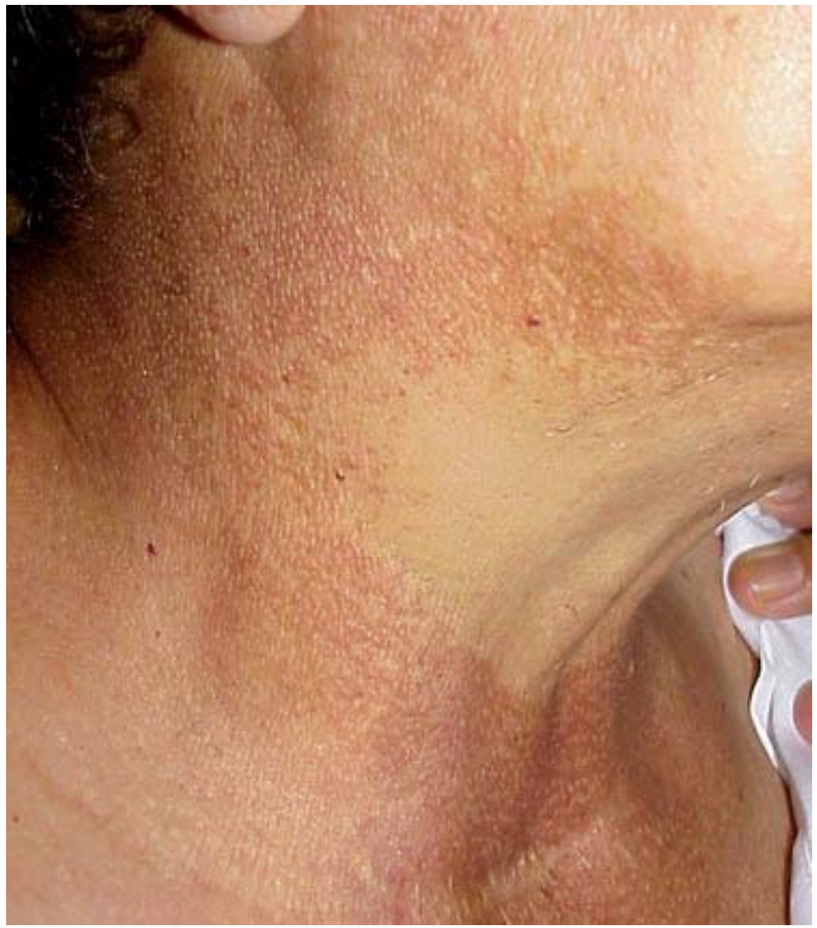
+

- Dyspigmentation

+

- Epidermal atrophy

Often asymptomatic

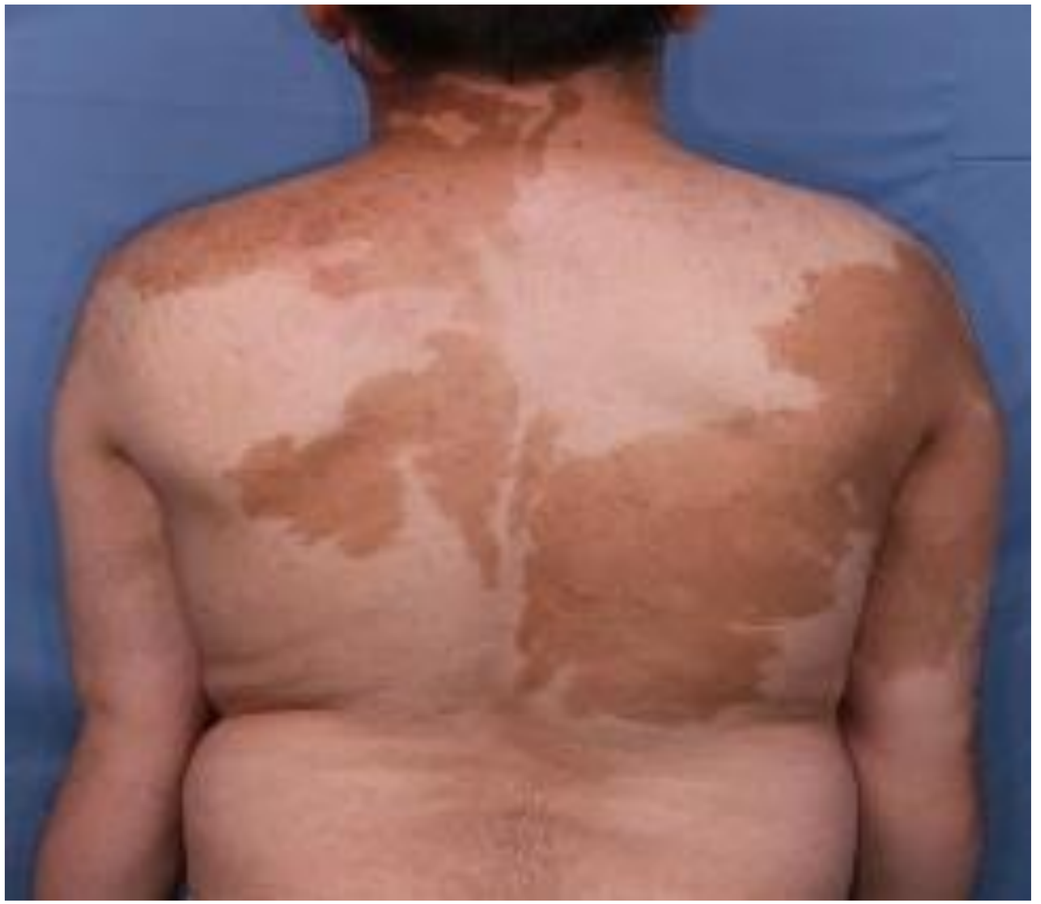


Management of Poikiloderma

- ✓ No specific treatment required
- ✓ C

Dyspigmentation

- Post-inflammatory hyperpigmentation or vitiligo-like hypopigmentation

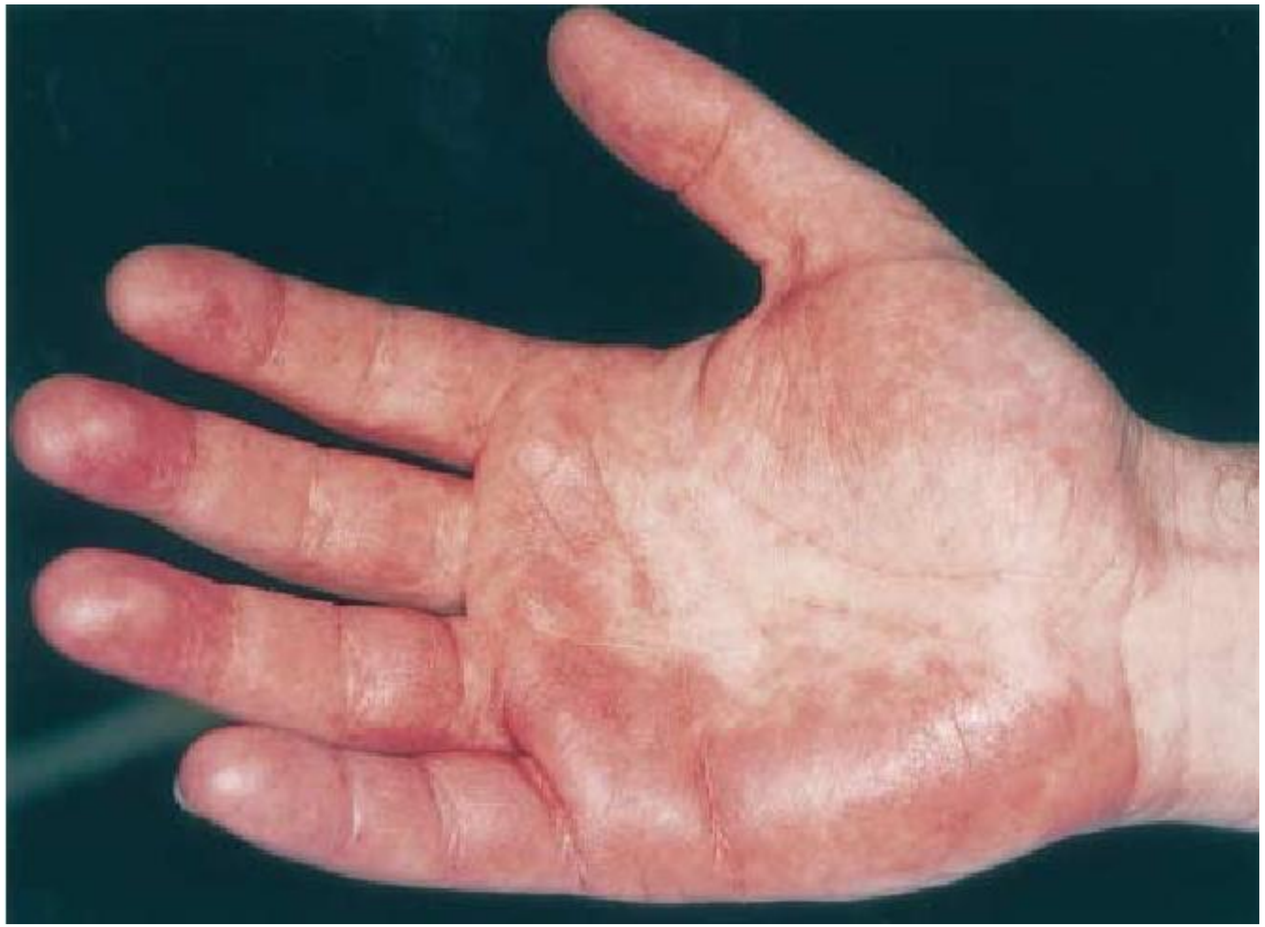


Management of Dyspigmentation

- ✓ Use topical steroids if erythema co-exists suggesting active GVHD
- ✓ Low threshold for skin biopsy!

Acral erythema

- Erythema
- Oedema
- Pain (can appear out of proportion to clinical signs)
- Hyperkeratosis

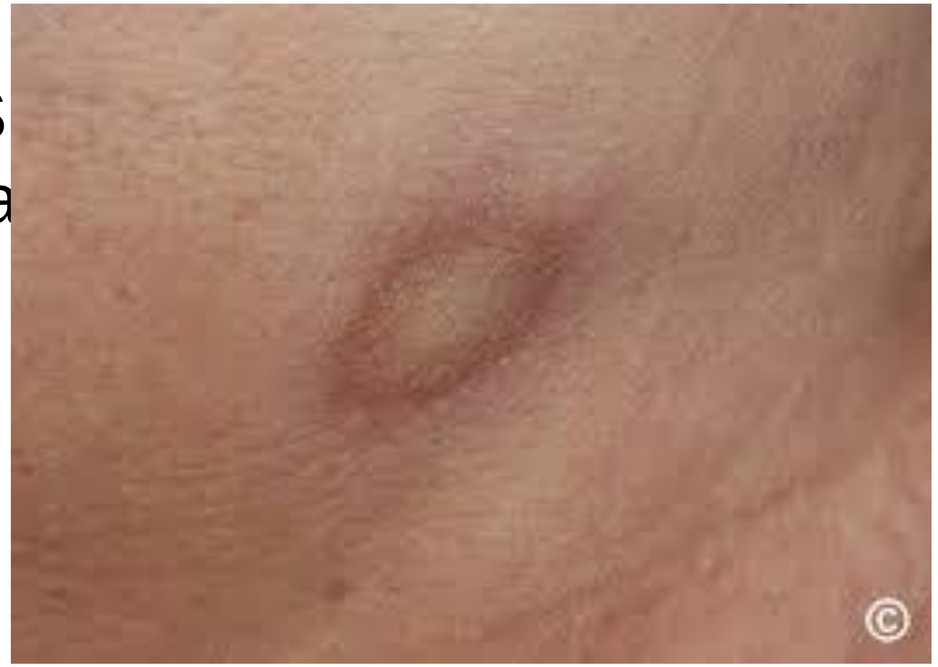


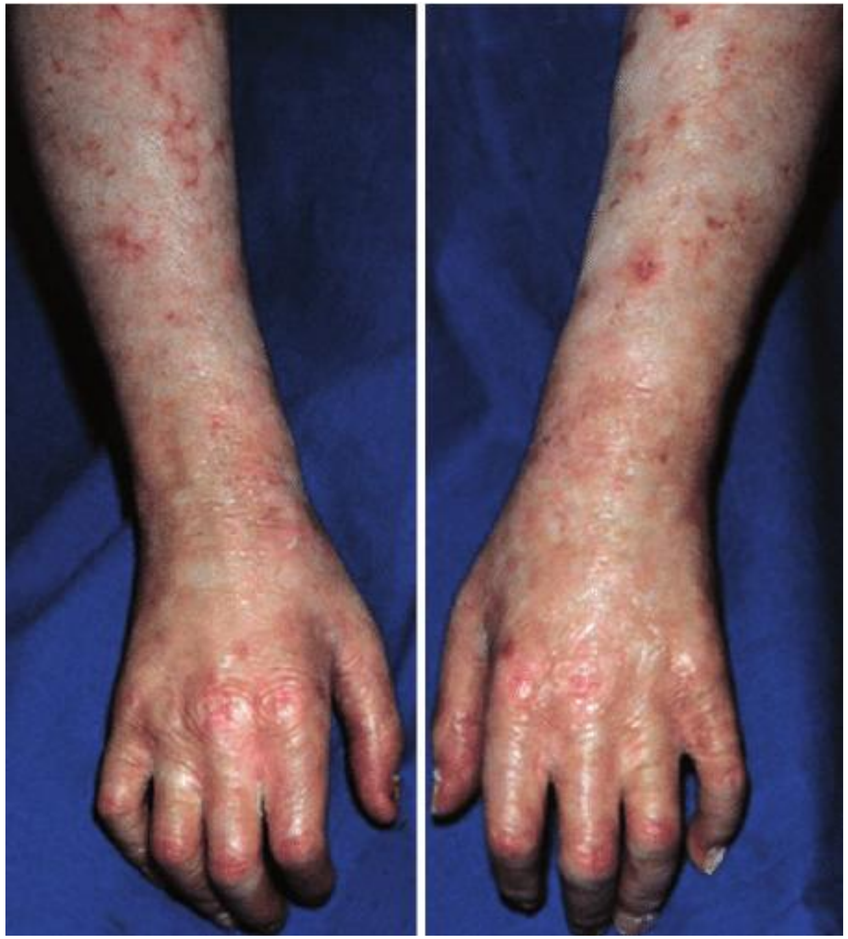
Management of Acral erythema

- ✓ Super-potent to keratosis
- ✓ Consider oral s

Morphoea / Sclerodermoid

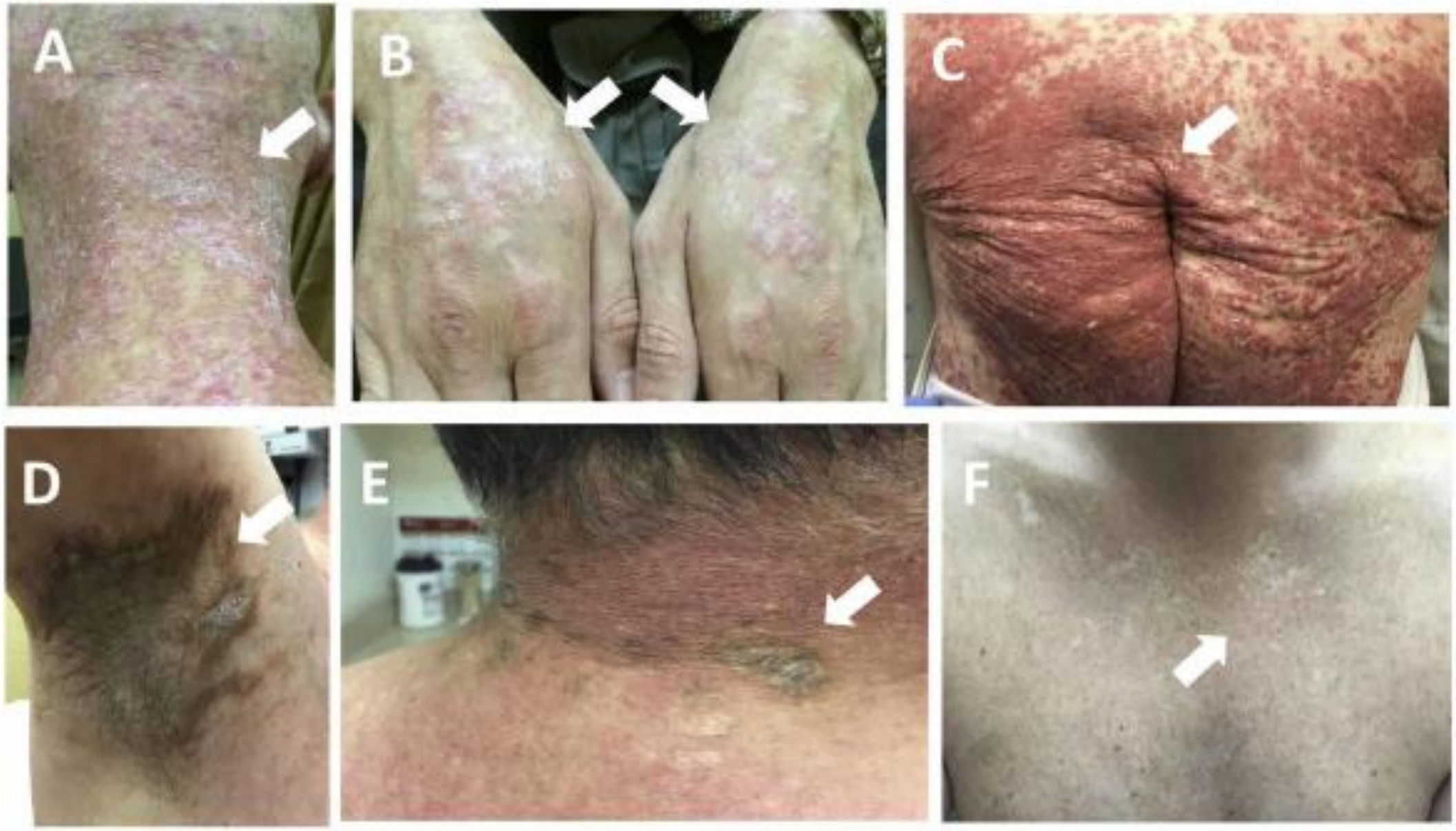
- S
pa



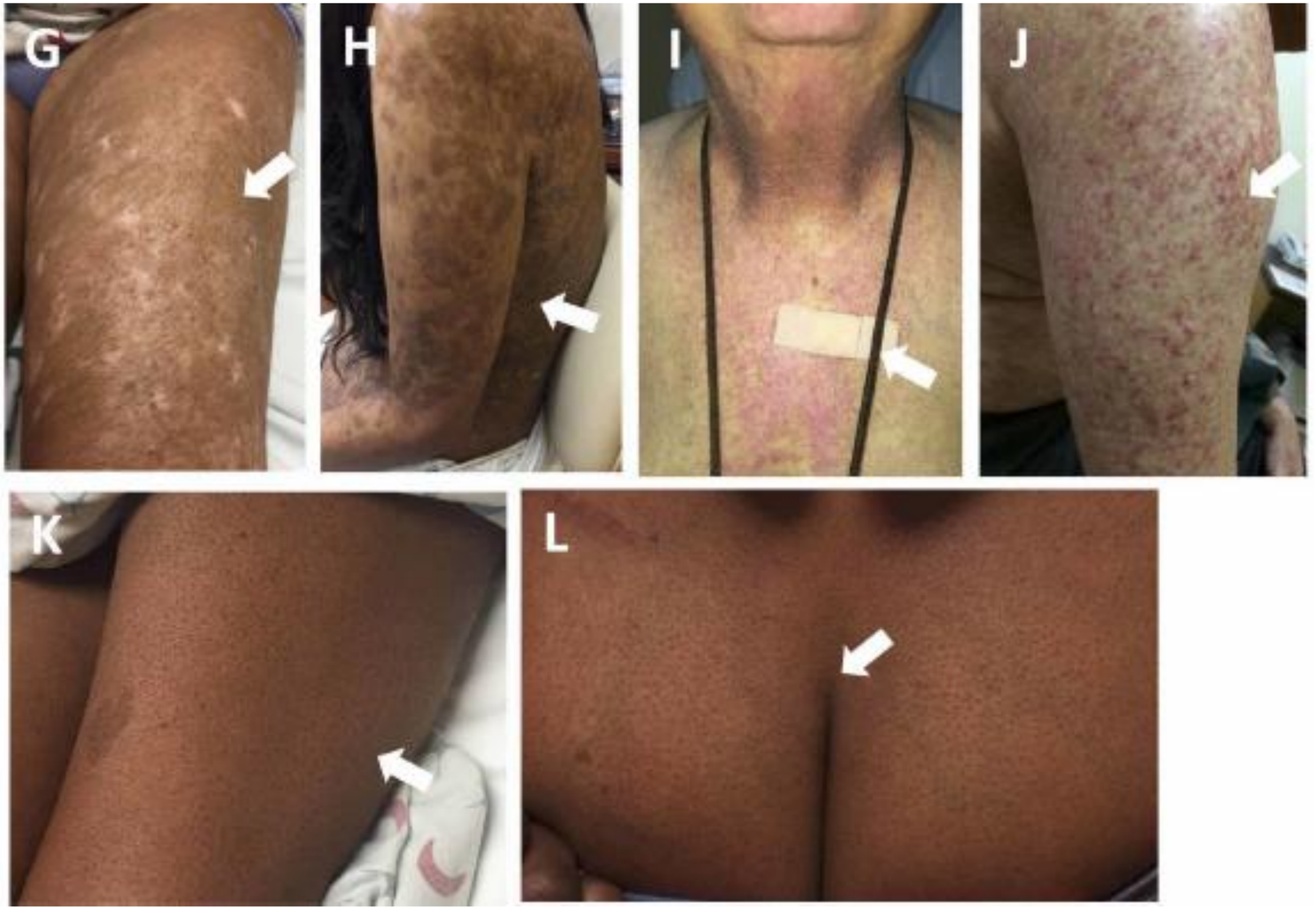


Management of Morphoea/ Sclerodermoid

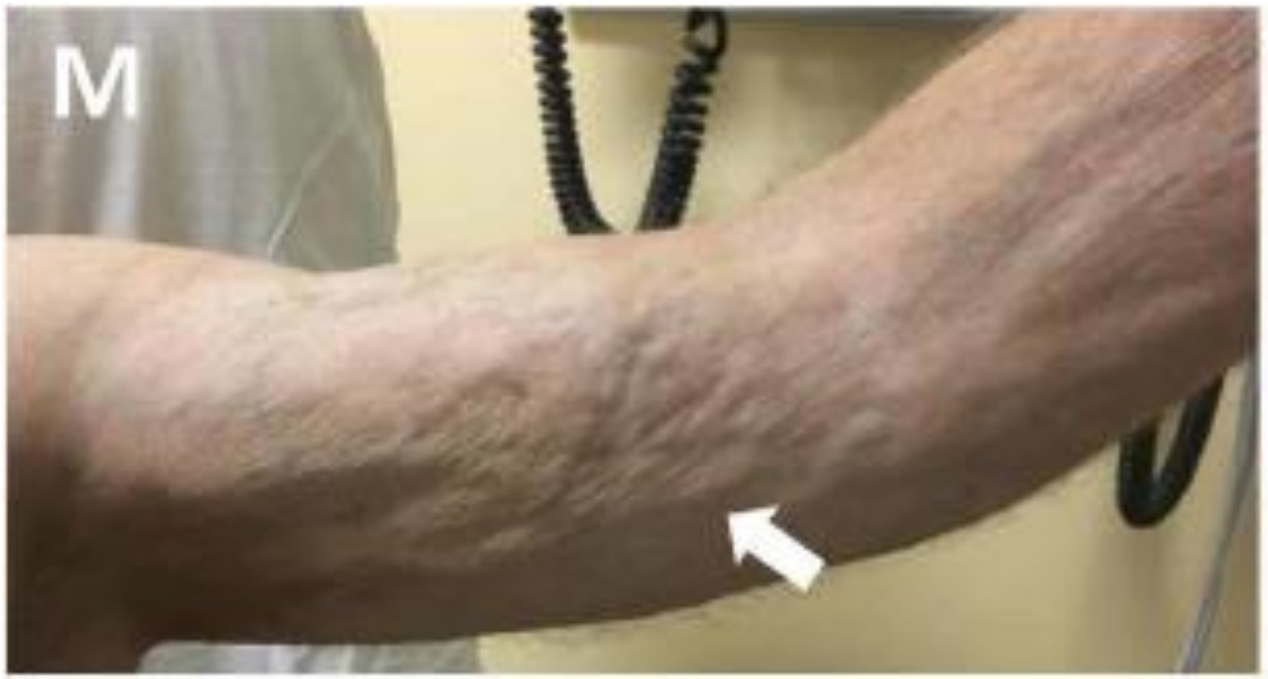
- ✓ If superficial consider PUVA or UVA1 phototherapy
- ✓ If deeper +/- other organ involvement, consider increased immunosuppression or extracorporeal photopheresis
- ✓ Consider referral to physiotherapist / podiatry / orthotics

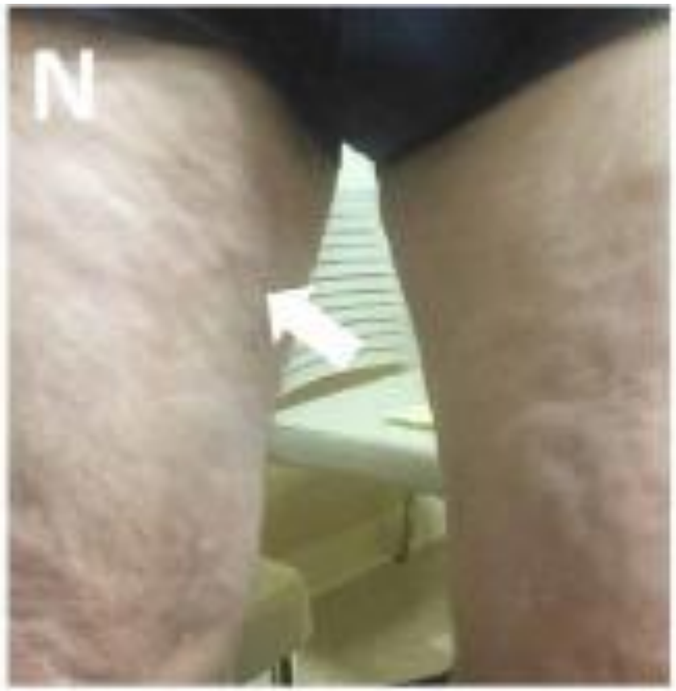


A, B: lichen planus-like; C: papulosquamous-like; D: lichen sclerosus-like; E: morphea-like; F: dyspigmentation;



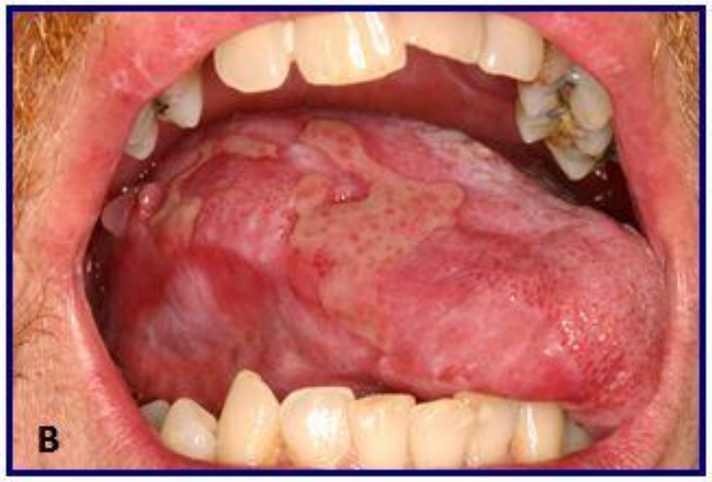
G, H: dyspigmentation; I, J: poikilodermatous; K, L:





M, N: dermal and subcutaneous skin changes

Mouth and chronic GVHD (oral GVHD)



- A topical steroid gel or cream
- An oral rinse containing dexamethasone, budesonide, tacrolimus

pical treatment with pilcarpine and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Case Presentation 1 : An adolescent (17 year old) male patient with acute lymphoblastic leukemia (ALL) Post-HSCT/ Chronic GvHD (Lung)

- Five months after transplant , patient is immunosuppression free.
- Bone marrow is in complete remission.
- He presented with Dry eye symptoms(eye drops >3 per day) without vision impairment. (GvHD score 2)/ **keratoconjunctivitis sicca**
- No response to artificial tears, gels and Cyclosporine A ophthalmic drop
- No response to punctal occlusion
- Finally he Underwent Partial tarsorrhaphy

Case Presentation 1 : An adolescent (17 year old) male patient with acute lymphoblastic leukemia (ALL) Post-HSCT/ Chronic GvHD (Lung)

13 months after transplant he presented with:

Dyspnea and dry cough

Severe painful ulcerations of mouth accompanied with lichenoid changes

Case Presentation 1 : An adolescent (17 year old) male patient with acute lymphoblastic leukemia (ALL) Post-HSCT/ Chronic GvHD (Lung)

Spiral Chest CT Scan: Focal infiltration

Pulmonary Function Test: FEV1 40%

BAL: No infection

Severe chronic lung GvHD

Case Presentation 1 : An adolescent (17 year old) male patient with acute lymphoblastic leukemia (ALL) Post-HSCT/ Chronic GvHD (Lung)

Methylprednisolon 1mg/kg

FAM+LABA

Case Presentation 1 : An adolescent (17 year old) male patient with acute lymphoblastic leukemia (ALL) Post-HSCT/ Chronic GvHD (Lung)

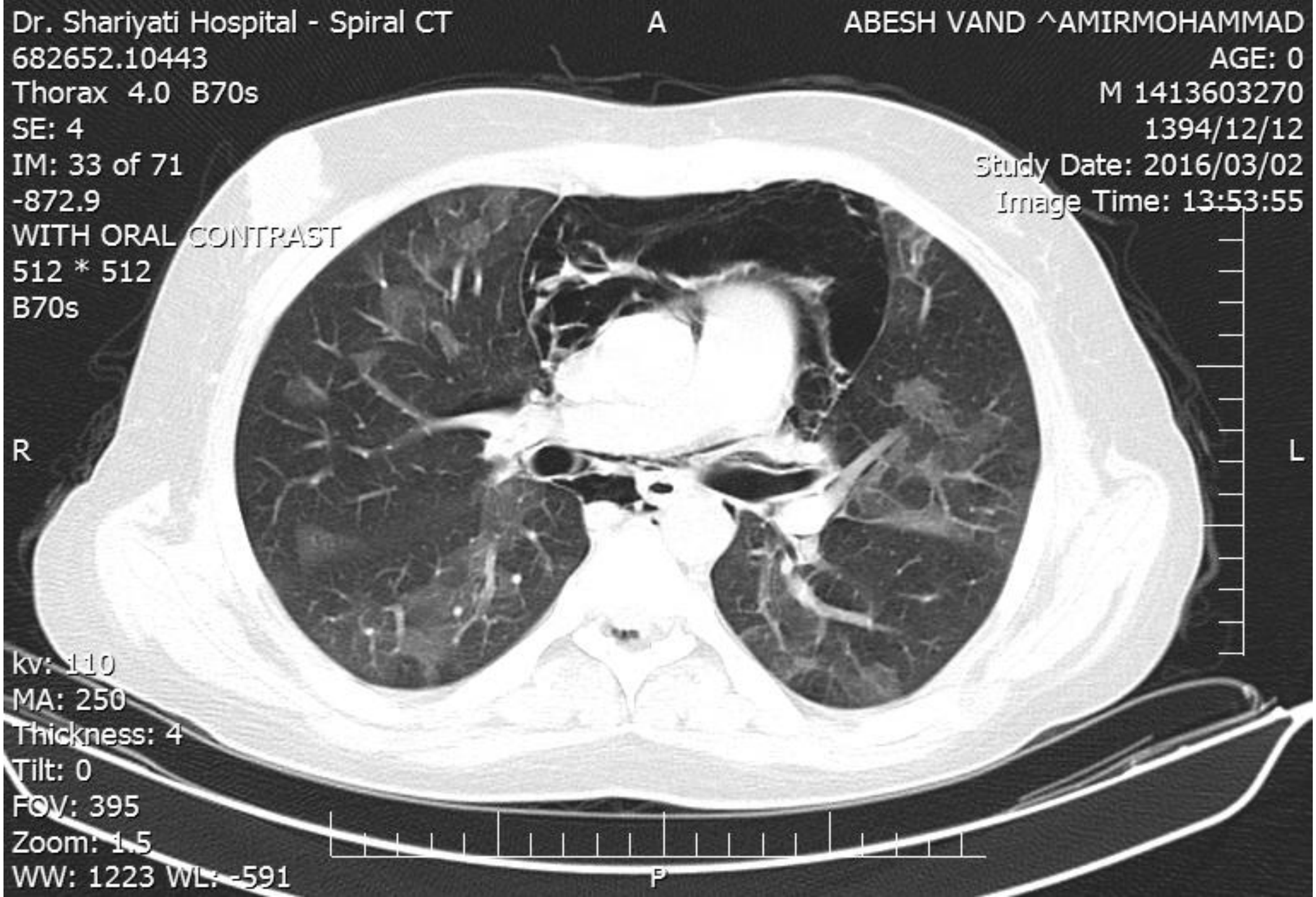
One week after starting Methylprednisolon, patient presented to emergency room with dyspnea and subcutaneous emphysema on neck and upper chest, no change in mouth ulcerations.

PFT: FEV1:

Air leak syndrome

This phenomenon (air leak syndrome) controlled by supportive care.

Next step? Ruxolitinib? Ibrutinib?


Dr. Shariyati Hospital - Spiral CT
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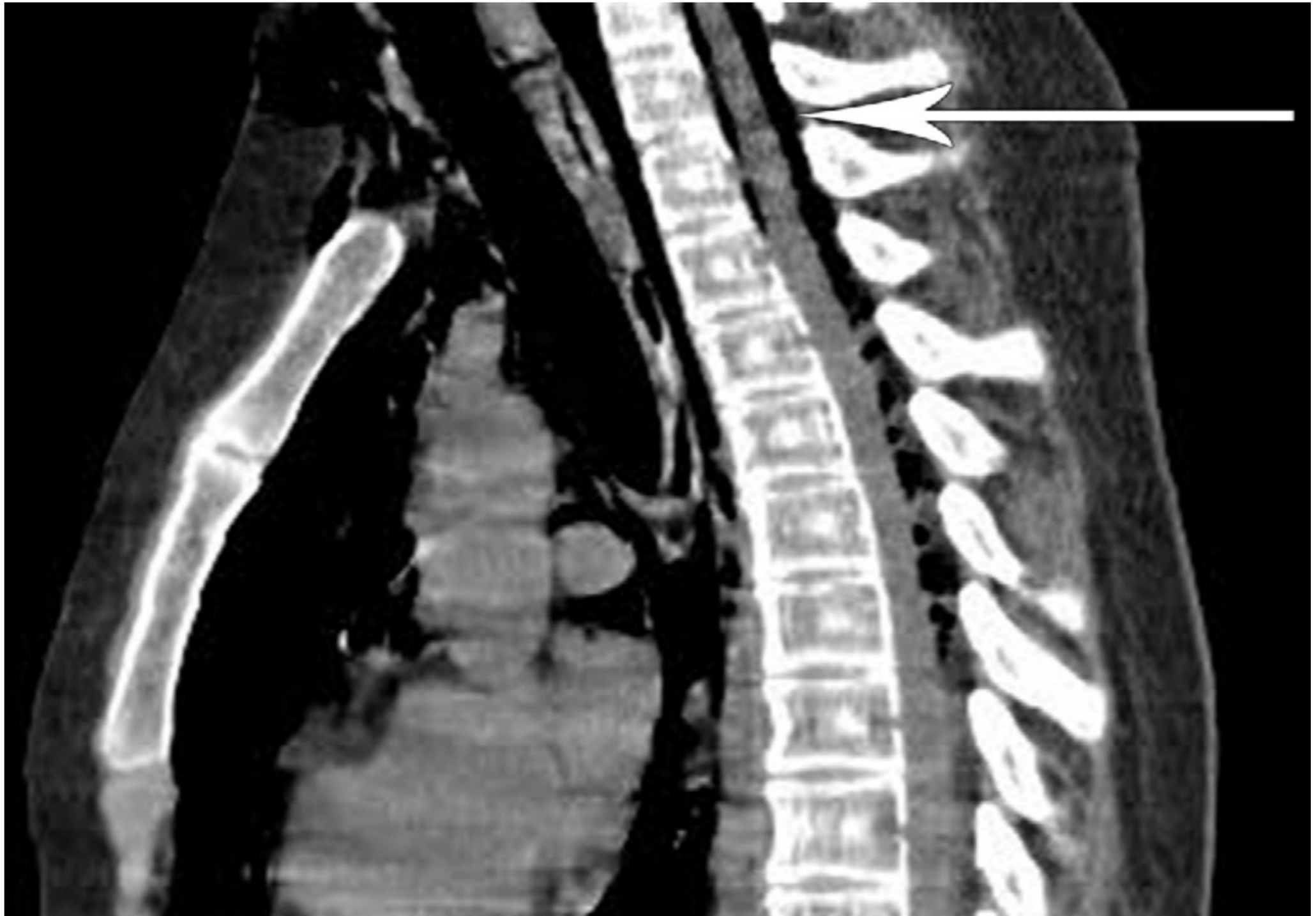


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Dr. PORGHARIB

Rehailitation

Rehabilitation

- topical treatments for skin GVHD as well as antidiarrheal therapy for patients with gastrointestinal GVHD, should be implemented routinely in clinical practice.

- Given the potential risk of functional decline, physical therapy and rehabilitation are also essential components to maximize the QOL and functioning of patients with acute GVHD.

- steroid myopa-thy in patients with acute GVHD is as high as 41%. Studies have shown that patients with acute GVHD have baseline impair-ments in their function, which are worsened within 14 days of receiving corticosteroid therapy.

- consultation with physical therapy, occupational therapy, and physical medicine and reha-bilitation to closely monitor

Rehab

- lower extremity edema and fluid retention due to corticosteroid use, poor nutrition and hypoalbuminemia, and their inflammatory state from acute GVHD.

- future therapies for acute GVHD, including probiotics, nutritional supplements, and fecal microbiota transplantation, are currently being tested in clinical trials

In the Name of God

CLINICAL CARE OPTIONS® ONCOLOGY

Rehabilitation & Exercise intervention in BMT & GVHD

Mohammad Hosein Pourgharib, M.D.

Associate Professor of Sports & Exercise Medicine

Shariati Hospital

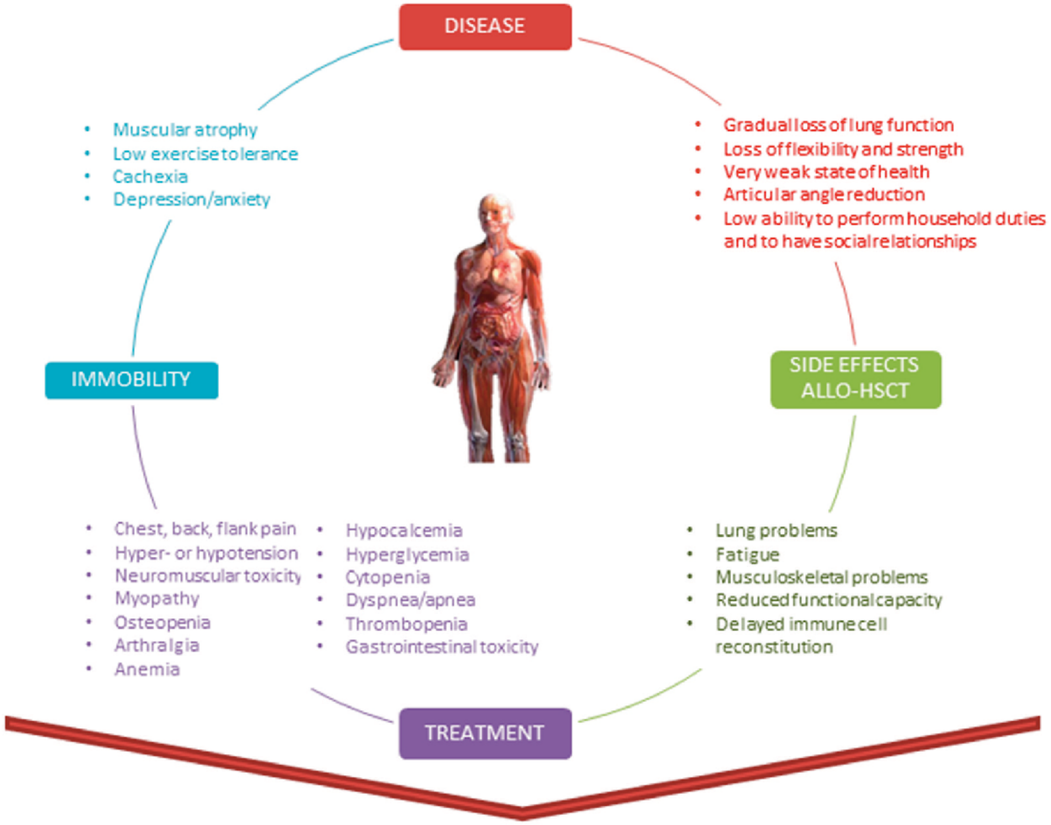
Tehran University of Medical Sciences

Challenges and Shortcomings of Research on Rehabilitation for cGVHD

- Challenges in Studying Rehabilitation Issues in cGVHD
  - Chronic GVHD has not traditionally been a **focus of rehabilitation** (compared with stroke, spinal cord injury, amputation, etc)
  - **Polymorphic clinical presentation**, so outcome measurements and standardization of trials is difficult
  - Patient populations are essentially **limited to tertiary care centers** with a BMT program
  - BMT physicians **may not be familiar with rehabilitation physician** skill sets, may not collaborate frequently

Challenges and Shortcomings of Research on Rehabilitation for cGVHD

- Examples of Topics in cGVHD Rehabilitation Needing More Research
  - Effects of **aerobic exercise** on reversing cGVHD
  - Bracing and/or splinting trials for sclerotic cGVHD
  - **Inpatient rehabilitation** and the benefits of multidisciplinary assessment
  - Prevalence of **steroid myopathy** and its impact on patient function and health
  - Correlation between loss of physical function and **hospital readmission**



aGVHD

- Liver
- Gastrointestinal tract
- Skin

cGVHD

- Eyes
- Nerves
- Mouth
- Heart
- Lungs
- Hematopoietic and immune systems
- Liver
- Gastrointestinal tract
- Skin
- Nails
- Tendons
- Skeletal muscle
- Joints
- Bones

ain clinical features of acute (aGVHD) and chronic graft-versus-host disease (cGVHD). Abbreviation: allo-HSCT

Common Rehabilitation Issues in cGVHD

Organ	Problem	Intervention
Skin/fascia	Sclerodermatous contractures	OT for ROM and strengthening, splinting, iontophoresis. Surgery likely ineffective and may have negative outcomes.
Muscle	Myopathy	PT for fall prevention and strengthening. Bracing for weak muscles. Adaptive equipment (canes, walkers) as indicated.
Bone	Osteoporosis	Core stabilization, bracing for pain or stability
Peripheral nervous system	Peripheral neuropathy	Bracing for motor weakness, nerve stabilizing agents for pain, wound prevention (proper footwear, frequent skin checks)
Cardiopulmonary	Physical deconditioning	Exercise program (possibly through PT), consider pulmonary or cardiac rehab for specific issues in these organ systems

OT indicates occupational therapy; ROM, range of motion; PT, physical therapy.

Exercise as an Adjuvant Therapy for Hematopoietic Stem Cell Mobilization

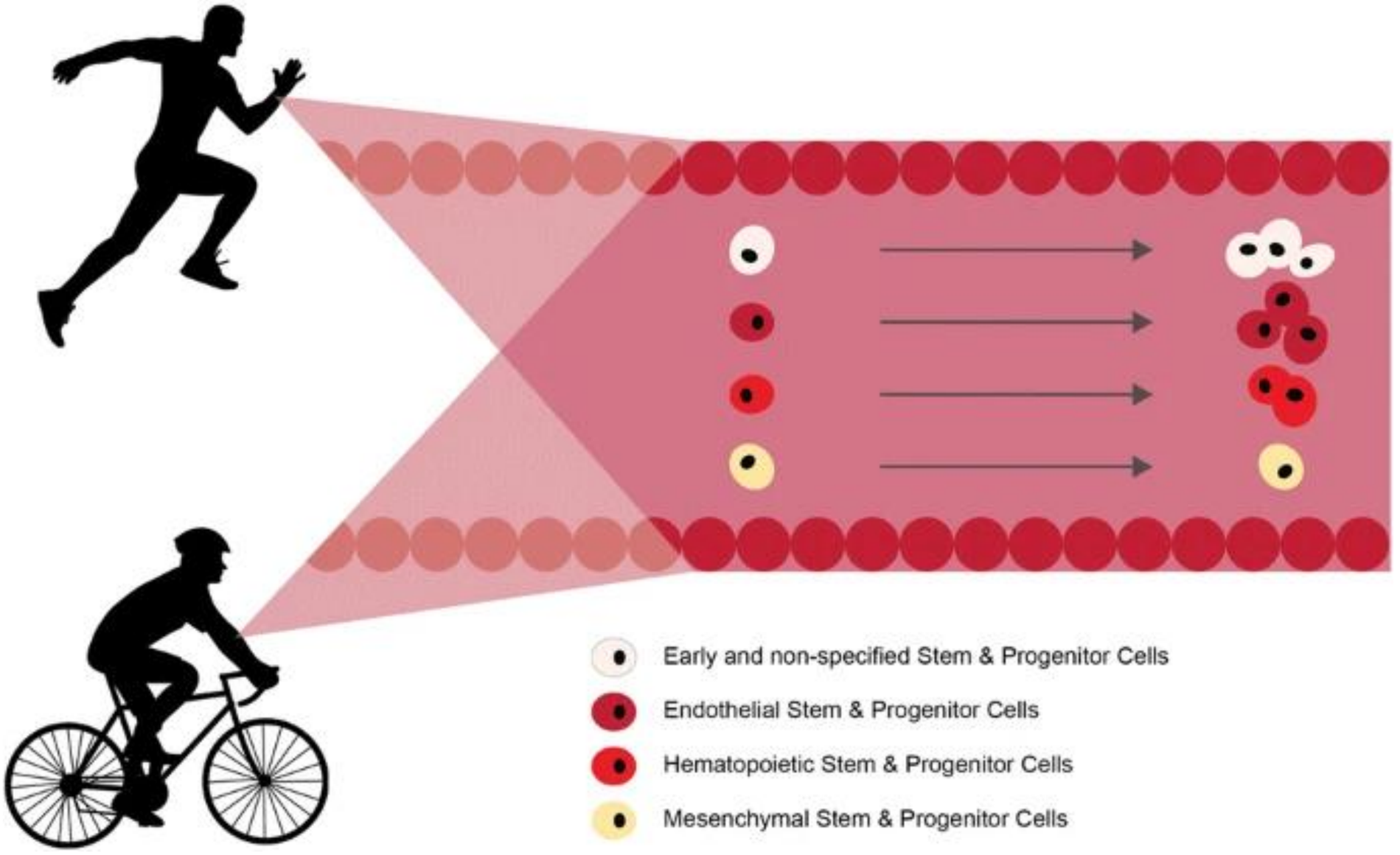
- HSPC collection protocols rely on pharmacological agents to mobilize hematopoietic stem cells (HSPCs) to peripheral blood.

- Limitations including variable donor responses and long dosing protocols merit further investigations into adjuvant therapies to enhance the efficiency of HSPCs collection.

- Exercise, a safe and feasible intervention in patients undergoing HSCT, has been shown to **robustly stimulate HSPC mobilization** from the bone marrow.

Stem Cells International Volume

Acute Exercise-induced Mobilization of Stem Cells



Future Perspectives

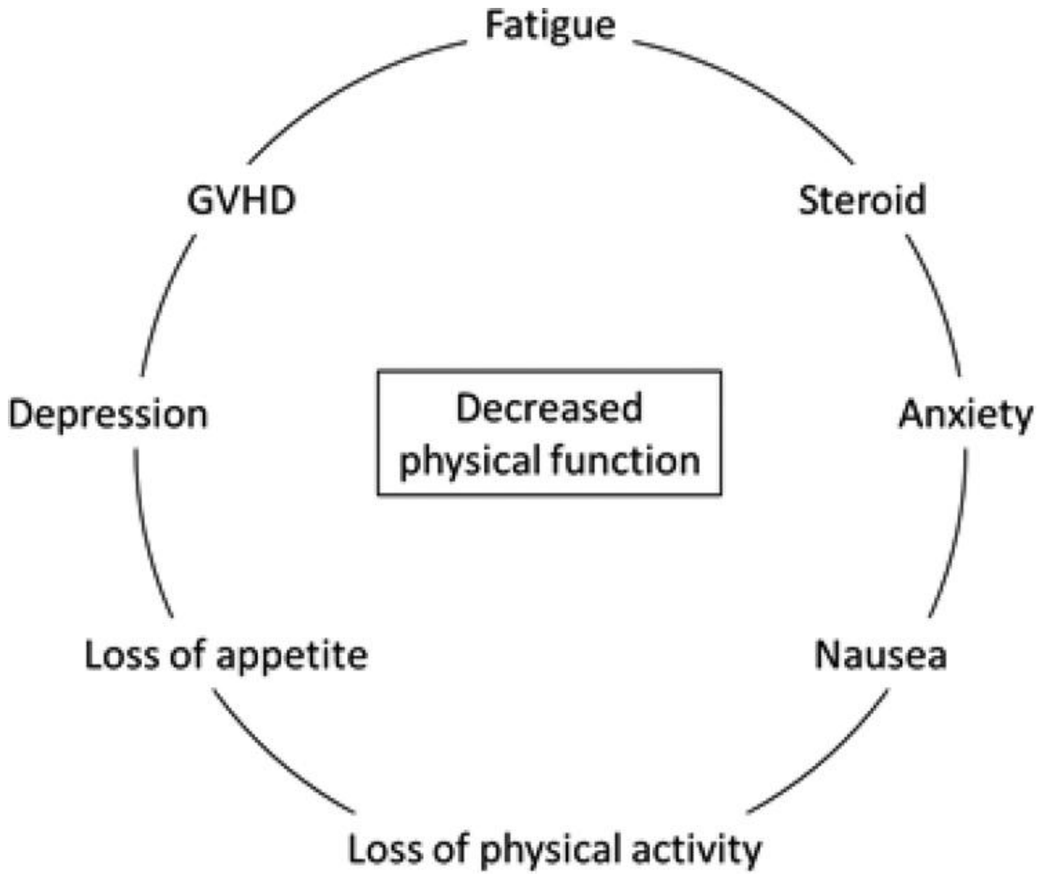
- **First**, the precise **parameters of exercise need to be better defined**. The optimal mode, intensity, and duration of exercise for maximal mobilization of HSPCs need to be established,

- **Second**, a better understanding of the **mechanisms responsible** for exercise-induced mobilization is needed.

- **Finally**, the efficacy of HSPCs mobilized by exercise needs to be **established in the transplantation setting**

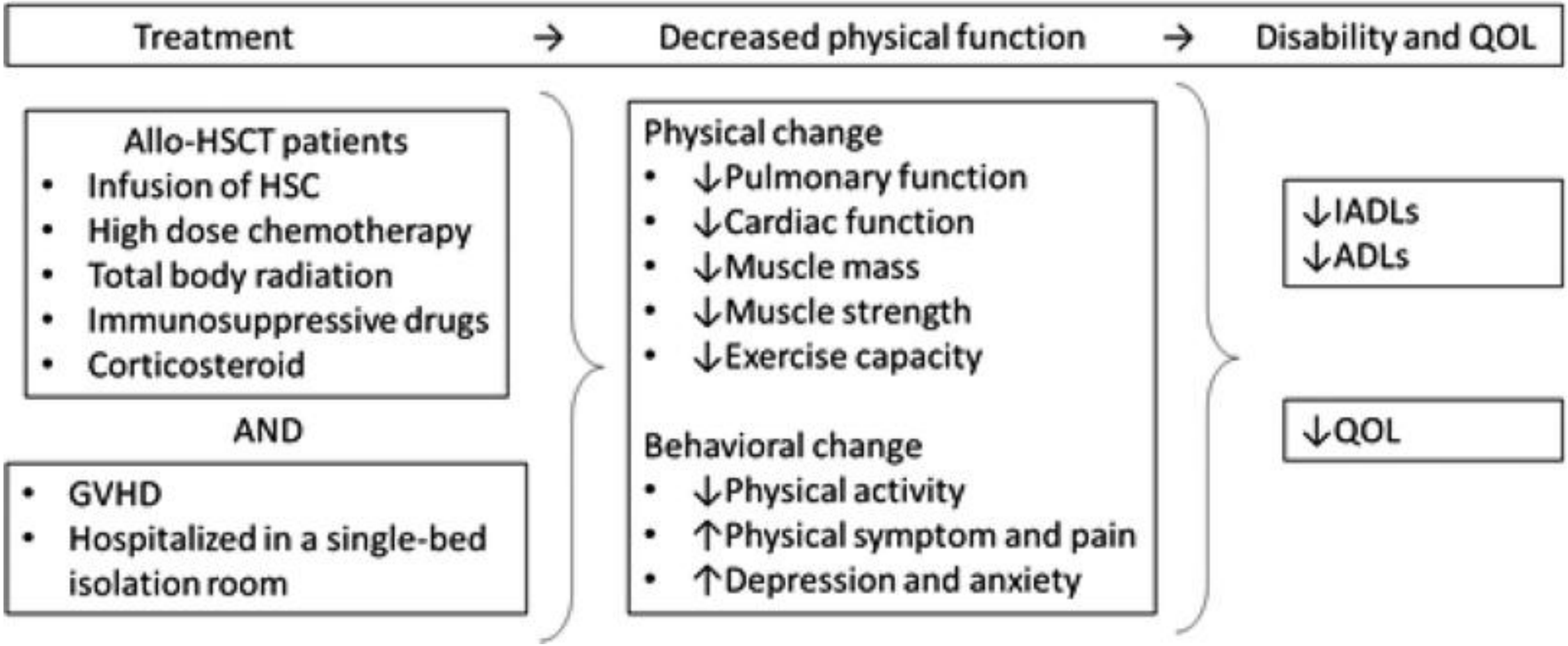
Stem Cells International Volume 2016, Article ID 7131359

The Benefit of Exercise in Patients Who Undergo Allogeneic Hematopoietic Stem Cell Transplantation



2019 The Journal of the International Society of Physical and Rehabilitation Medicine

Decrease in physical function, disability, and QOL in patients with allo-HSCT after treatment



Physical exercise before admission, during hospitalization, and after discharge

- Allo-HSCT patients **require physical exercise** to prevent a decrease in physical function or improve physical function.

- The **use of corticosteroids** and decreases in physical activity post-HSCT seem to be related to decreases in physical function.

- These patients experience **nausea, loss of appetite, and GVHD**, and tend to experience a **decline in nutritional status and weight**, which leads to muscle loss and loss of physical vitality.

- Therefore, future studies on the effects of **nutritional therapy combined**

is possible that **muscle strength** and **physical activity** could have a relationship with mortality in these patients.

- Future studies should investigate these possible relationships.

- Future **long-term follow-up studies** focusing on the long-term physical function and overall QOL are needed.

- The **survival rates** of allo-HSCT patients have been improving, with many allo-HSCT patients living longer than those in the past.

- Thus, the maintenance of physical function, and its relationship to physical exercise, should be investigated in long-term survivors of allo-HSCT in addition to inpatient populations.

- The review suggests that physical exercise is beneficial for the **physiological**, **psychological**, and **psychosocial health** of allo-HSCT patients.

- Clinicians should encourage patients to perform physical exercise **before, during, and after transplantation**, and physical exercise **should be integrated** into the conditioning and recovery plans for all allo-HSCT patients.

Rehabilitation after Allogeneic Haematopoietic Stem Cell

- Acute Rehabilitation as an Inpatient
- Acute Rehabilitation as an Outpatient
- Acute Rehabilitation as an Inpatient Later in the Time Course
- Rehabilitation with Chronic GVHD

Cancers **2021**, 13, 6187. https://doi.org/10.3390/cancers13246187

Acute Rehabilitation as an Inpatient

- Malnutrition
- Muscle Loss
- Risk of Infections
- Psycho-Oncological Aspects
- Psychosocial Aspects

Acute Rehabilitation as an Inpatient

- Occurs **around day +25 (ranging between 19 and 35 days)** after the transplantation

- Suffer from the same side effects and discomforts as other cancer patients soon after therapy, such as:

  - fatigue, nausea, vomiting, neurocognitive deficits, and perhaps diarrhoea.

transplantation ward, mainly in their **single isolation room**, usually **lying in their bed**;

Muscle Loss

- their physical activities diminish dramatically (to 10–15%) and their muscles shrink.

- Additional drugs like **corticosteroids and CNIs** cause myopathy, which is then aggravated by the polyneuropathy induced by several drugs (e.g., CNIs).

- Paradigmatic change has happened over the last 25 years, and after the first evidence of its benefits was published, **exercise was introduced on the transplantation wards**, and the patients are now motivated to exercise.

- Three different kinds of exercise should be encouraged for patients:
  - Endurance
  - Strength
  - Balance

an **individualised training program**.

- **Whole body vibration** has been introduced without major side effects on the transplantation ward;
- it increases the muscle tissue and improves functional capacity.
- It is also safe and effective in the rehabilitation setting as well, as are **Nordic walking, ergometric training, electro muscle stimulation (EMS), and low-weight training.**
- The main task during rehabilitation is to improve the patient's physical

- Special attention should be paid to the **climbing of stairs**, which is impaired by the aforementioned myopathy.

- One often neglected aspect is **balance**; patients with balance problems carry a high risk of falling, and osteoporosis leads to fractures.

- As infections should be avoided, training the **breathing muscles** is a further target of special exercise in this patient group.

- Because these patients are severely immunosuppressed, training in a group may be impossible because of the high risk of infections, which is why **individualised training** programs are preferable and should be offered.

Acute Rehabilitation as an Outpatient

- Outpatient rehabilitation in the first three months will primarily consist of **physical exercise**, as mentioned above, involving the training of strength, power, and balance.

- This should be done **at least twice a week** at two- to three-day intervals.

- An alternative is **web–based training programs,** which are individualised by the physiotherapists or sports scientists in the transplant centre.

- These programs can be adopted if the patient’s fitness is improving

Acute Rehabilitation as an Inpatient Later in the Time Course

- If patients come in for rehabilitation later as an inpatient in their **post-alloHCT time course (mainly on days +60–90),** then their recovery has started, accompanied by the main side effects, and patients are more capable of participating in their tasks in the rehabilitation clinic

- These patients can participate in **group exercise**, lectures, and eat in the clinic restaurant.

- If they have not engaged in an intensive outpatient sports programme after discharge from the transplant centre, they will still be struggling with **muscle loss, weakness, and a certain amount of fatigue**.

Rehabilitation with Chronic GvHD

What role does the rehabilitation centre play?

- The **main goal** of a planned intensive rehabilitation period is **physical therapy**.

- The patients' **physical limitations** are what mainly prevent them from participating in their ADL.

- To achieve this goal, the therapist **should possess a great deal of experience** in treating this alloHCT complication in particular, especially in patients suffering from skin/fascia related GvHDs.

Rehabilitation with Chronic CVID

What role does the rehabilitation centre play?

- A list of possible interventions is:
  - Massage
  - breathing exercise
  - connective tissue massage
  - lymph drainage
  - polyneuropathy training
  - wraps
  - light therapy with UVA A and B
  - whole body vibration (WBV)

- Such cGvHD-associated impairments can affect the patients emotionally, and psychologically as well;
  - they **cannot move** as they used to (reduced performance),
  - can suffer from **shortness of breath** (which is extremely frightening),
  - their **appearance** is altered (hair loss, dyspigmentation),
  - **sexual activity** is impaired in cases of cGvHD of the genitals (in females and males).

- These problems also **require experienced psycho-oncologists** because their treatment differs from the follow-up care of “normal” oncology patients

- With longer and more frequent support during **a 3–4-week rehabilitation programme**, these discomforts can be dealt with effectively.

- In cases of severe cGvHD involving severe impairments, rehabilitation **twice a year**, or at the very least once a year, helps these patients.

- Side effects of the CNIs are damage to the vessel endothelia, which leads to **hypertension**, and **vascular diseases of the heart and brain**.

- These impairments should be diagnosed and handled again mainly through exercise during follow-up care.

- The clinical manifestation has implication for **patients' physical function**, limiting a patient's ability to carry out activities of daily living and subsequently reduces the quality of life.

- Impairments in the physical domain is a result of both the **disease** itself and its **treatments**.

- Unfortunately, **usage of glucocorticoids** is associated with a variety of side-efects, especially at higher doses and with longer duration of therapy,
  - such as **osteoporosis**, **osteonecrosis**, **diabetes** and
  - **myopathy** with weakness primarily found in the proximal lower muscles, with particularly the pelvic girdle muscles being involved.

- In view of the poor treatment respond and the toxic effects of the GvHD therapy, **new supportive strategies** that will help maintain or even improve patients' quality of life are needed.

- Such supportive therapies should particularly target the physical domain, hence, reducing impacts on activities of daily living resulting in the **preservation of public participation and autonomy**

- A 2021 systematic review yielded that **exercise interventions** may be beneficial on **physical functioning and quality of life** in patients undergoing HSCT.

- The findings of **the positive effects of exercise on HSCT** patients are supported by another review which found beneficial effects for muscle strength and physical fitness.

- Specifically in patients receiving an allo HSCT, randomized controlled studies showed that exercise is capable of **counteracting the negative consequences of cancer** and its treatment and may **improve survival**

- Pre-clinical findings in a chronic GvHD murine model under standard immunosuppressive therapy suggest beneficial effects of **exercise on survival, clinical course of GvHD and on physical capacity** in the exercising mice group compared to control animals.

- Moreover, the exercising mice showed **lower TNF-α and IL-4 levels** after 12weeks post transplant, reflecting **a weaker inflammatory state.**

- These findings give first insight on how exercise may affect the clinical and biological course of GvHD patients.

- A prospective study authored by Morishita et al. showed that the cumulative corticosteroids dose is associated with **weak handgrip and knee extension**.

- This is in line with recent findings of a small single-arm cohort study by Ngo-Huang et al. , who investigated acute GvHD patients on high-dose steroids and their decline in objective functional tests.

- They found a significant association between cumulative corticosteroid dose and the following functional tests: **6min walk test, hip flexors and knee flexors strength, manual muscle testing strength, sit to stand test.**

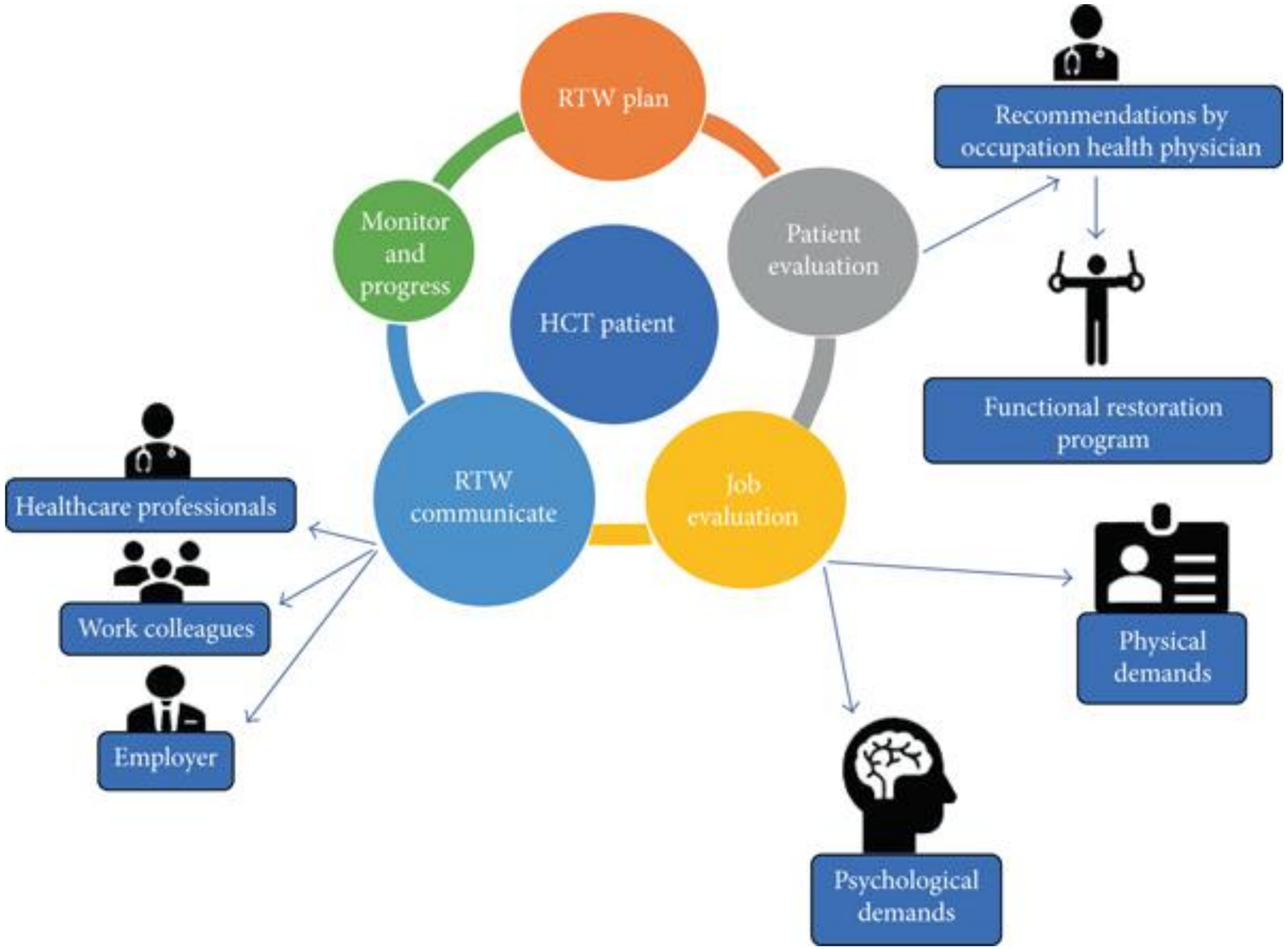
- In terms of the timing of the decline, weakness can be detected **as early as day 14**, suggesting that **early supportive interventions** are needed to mitigate these changes.

- Interestingly, Morishita et al. found that physical therapy is positively associated with physical function, indicating that exercise may be capable **of ameliorating the detrimental effects of GvHD** and its treatment.

Combined exercise and nutritional support

- it is likely that a **combination of an exercise and nutritional** intervention will be of greater benefit than one intervention in isolation.

Understanding the Process and Challenges for Return-to-Work Post-Hematopoietic Cell Transplantation from a Musculoskeletal Perspective: A Narrative Review



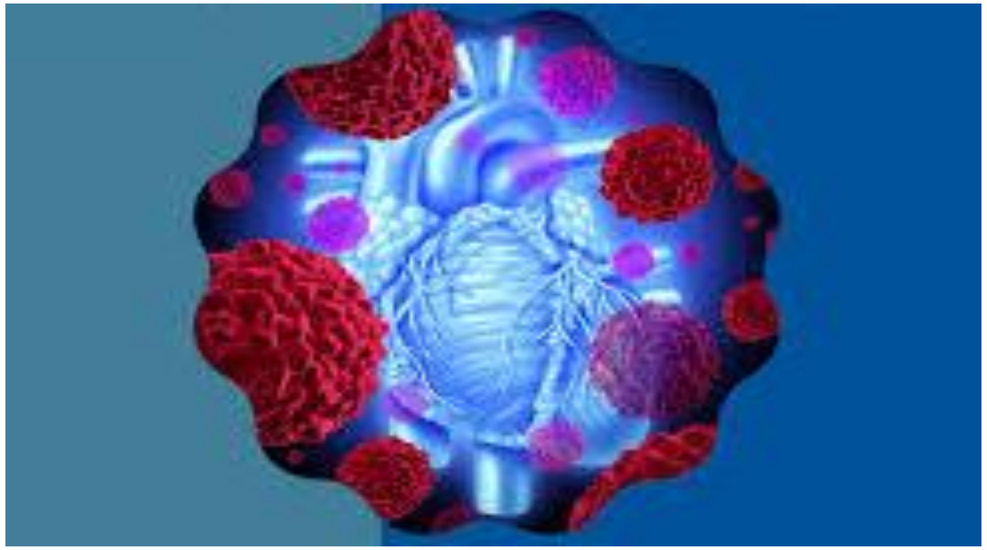
Occupational □erapy International Volume 2021, Article ID 5568513,

Physical exercise before admission, during hospitalization, and after discharge

Thanks

Cardiovascular considerations IN HSCT

Azin Alizadehasl, md, FACC, FASE; ECHOCARDIOLOGIST; Cardio-oncologist;
Cardio-oncology department, rajaei heart center



Cardio-Oncology Department and Research Center

Rajaie Cardiovascular Medical & Research Center, Tehran, Iran

Haematopoietic stem cell transplantation (HSCT)

- HSCT constitutes a potentially curative therapeutic option for many hematological malignancies (1.5 million patients received HSCT in 2019).

- Improvements in HSCT techniques and **supportive strategies** have markedly decreased treatment-related mortality

- Prevalence of all cardiovascular complications in post HSCT patients is about 17% (more common in late phase)

risk factors for HSCT-related Cardiovascular toxicity

1. HSCT type (higher risk after allogeneic HSCT)

11. Multiple uncontrolled CVRF (specially DM & HTN)

111. Pre-existing CV disorders (AF or atrial flutter, sick sinus syndrome, ventricular arrhythmias, CAD, MI, moderate-to-severe VHD, and HF or LVEF < 40%)

1V. Direct cardiotoxic effects of anticancer therapies received prior to and during HSCT (anthracycline, tyrosine kinase inhibitors and other molecular targeted agents combined induction regimen, mediastinal RT, total body irradiation, or cyclophosphamide-based conditioning regimen)

V. Development of graft vs. host disease (GVHD, thrombotic microangiopathy)

VI. Sepsis

TABLE 18-3 Risk Factors for Cardiovascular Complications After Hematopoietic Cell Transplantation

1. Signs or symptoms of angina and/or heart failure
2. Significant abnormalities on electrocardiography (arrhythmias, heart block, Q waves)
3. Left ventricular dysfunction (left ventricular ejection fraction $<40\%$)
4. Abnormal cardiac biomarkers (troponin, brain natriuretic peptide)
5. Prior cardiotoxic cancer therapy (anthracyclines, proteasome inhibitors, cyclophosphamide, chest radiation)
6. History of heart failure, cardiomyopathy, or at least grade II diastolic dysfunction
7. History of myocardial infarction within 30 days
8. History of unexplained syncope
9. History of aortic or mitral valve stenosis
0. History of pulmonary hypertension

Screening tests

-All patients should be screened with : Clinical history

12-lead ECG

TTE (echocardiography)

CXR

NP assessment

-**TTE** is a core component of the pre-HSCT assessment to detect undiagnosed CVD, stratify CTR-CVT(Cancer therapy-related cardiovascular toxicity) risk and optimize pre-existing CV conditions

- Patients with high-risk features should be referred to a cardio-oncologist for further evaluation and risk factor modification

- A dose-dependent association between pre-transplantation exposure to **anthracyclines** and the incidence of **CHF** in HSCT patients is shown accompanied with other cardiac complication such as **hypertension, ischemia and arrhythmia**.

- **The American Society of Clinical Oncology (ASCO) define risk factor for cardiotoxicity as dose of *doxorubicine* ≥ *250 mg/m2 or epirubicin* ≥ *600 mg/m2.***

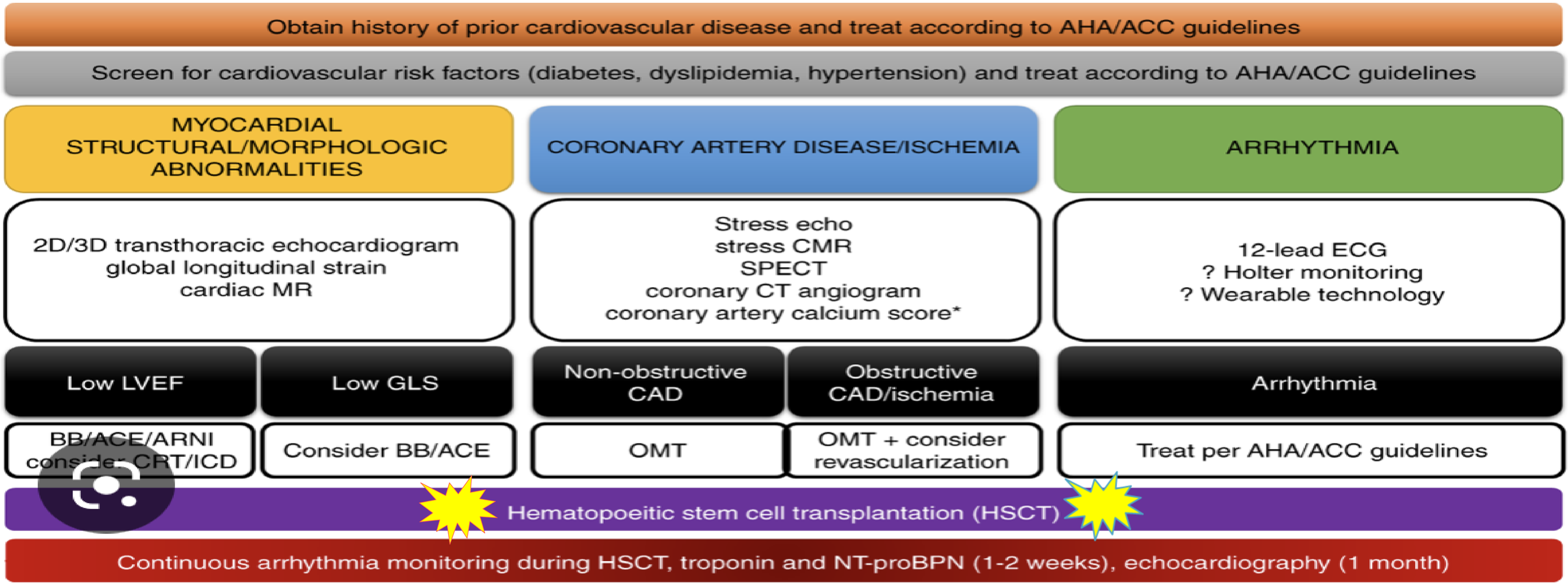
TARGETED THERAPY

These agents are related to several cardiovascular complications such as pulmonary hypertension, myocarditis, pericarditis, arrhythmia, myocardial ischemia and vascular events

Among different types of these agents ,TKI have a certain relation with cardiovascular complications and are used as both traditional chemotherapy and in post HSCT pts as maintenance therapy to prevent relapsing

Radiation

- Previous chest radiotherapy increases the risk of cardiomyopathy, cardiac dysfunction and CAD in post HSCT pts
- Exposure dose ≥30 Gy is a risk factor for radiotherapy-induced cardiotoxicity
- **Anthracycline at a lower dose can cause cardiotoxicity by additional low-dose radiotherapy (<30GY)**


Obtain history of prior cardiovascular disease and treat according to AHA/ACC guidelines
Screen for cardiovascular risk factors (diabetes, dyslipidemia, hypertension) and treat according to AHA/ACC guidelines
MYOCARDIAL STRUCTURAL/MORPHOLOGIC ABNORMALITIES
CORONARY ARTERY DISEASE/ISCHEMIA
ARRHYTHMIA
2D/3D transthoracic echocardiogram
global longitudinal strain
cardiac MR
Stress echo
stress CMR
SPECT
coronary CT angiogram
coronary artery calcium score*
12-lead ECG
? Holter monitoring
? Wearable technology
Low LVEF
Low GLS
Non-obstructive CAD
Obstructive CAD/ischemia
Arrhythmia
BB/ACE/ARNI
consider CRT/ICD
Consider BB/ACE
OMT
OMT + consider revascularization
Treat per AHA/ACC guidelines
Hematopoeitic stem cell transplantation (HSCT)
Continuous arrhythmia monitoring during HSCT, troponin and NT-proBPN (1-2 weeks), echocardiography (1 month)

Cyclophosphamide

CONDITIONING REGIMENS & PARAMETERS OF CARDIAC RISK

- A high dose of >100 mg/kg is correlated with cardiac damage, the HF is dose-dependent and is reported at the rate of **8.5, 1.5, and 0%** of the pts treated with a total dose of **200, 120, and 100 mg/kg** , respectively

- Other Cardiac complications includes malignant arrhythmia, pericarditis and myocarditis

- Cyclophosphamide is also used in post HSCT patients as GVHD prophylaxis and this dose is lower than used in the conditioning.

Total body radiation

- ***Early and Late radiation induced cardiac complications.***

- ***HSCT following conditioning with radiotherapy causes excessive iron accumulation due to RBC transfusion and thus cardiomyopathy can be occurred by generating free radicals and reactive oxygen species (ROS).***

Fluid Overload as New Toxicity Category can affect the heart

- Patients who experienced weight gain ≥10% (grade 2) early during hospitalization experienced higher non-relapse mortality (NRM) and worse survival.

- Fluid toxicity had the greatest impact on NRM of all known causes.

- Further cardiac monitoring are needed to better prevent of complications.

In early surveillance, TTE monitoring is recommended in HSCT recipients at **3 and 12 months** as LVEF and GLS can decrease after transplant

- **High risk PTS need more and more monitoring:**

Allogenic HSCT, pre-existing CVD or multiple uncontrolled CV-RF, cancer treatment history (mediastinal or mantle field radiation, alkylating agents, >250 mg/m2 doxorubicin or equivalent, total body irradiation or cyclophosphamide-based conditioning regimen) and GVHD

Recommendation Table 22 — Recommendations for baseline risk assessment in haematopoietic stem cell transplantation patients

Recommendations	Class[a]	Level[b]
Baseline and serial CV risk assessment (3 and 12 months, then yearly) including BP measurement, ECG, lipid measurement, and HbA1c is recommended in HSCT patients.	I	C
Echocardiography is recommended in all patients before HSCT.	I	C
Baseline NP measurement should be considered before HSCT.[417,418]	IIa	C

BP, blood pressure; CV, cardiovascular; ECG, electrocardiogram; HbA1c, glycated haemoglobin; HSCT, haematopoietic stem cell transplantation; NP, natriuretic peptides.
[a]Class of recommendation.
[b]Level of evidence.

Early and late toxicities

- In the early phase following HSCT (during and first100 days), the most frequent CV event is AF, although some patients may experience HF , hypertension, hypotension, pericardial effusion or VTE

- Late toxicities include DM, dyslipidemia, metabolic syndrome, hypertension, HF, CAD, conductions disorders, and pericardial effusion.

GVHD

- Acute GVHD (30-70%) is associated with thrombosis and inflammatory myocardial and endocardial damage (myocarditis, HF, conduction abnormalities, arrhythmias and pericardial effusions)

- Chronic GVHD has been linked with increasing risk of hypertension, DM, and dyslipidemia (Metabolic Syndrome)

Cardiac GVHD

- GVHD have direct cardiotoxicity effect through donor T-cells infiltration in myocardium and indirect toxicity via cytokines release such as TNF-α and IL-2.

- TNF-α can affect muscle electrical activity, and reduces myocardial contractility.

- IL-2 is also associated to arrhythmia (tachyarrhythmia, bradyarrhythmia and high degree atrioventricular block).

- Post HSCT survivors who develop grade II-IV acute GVHD, have about nine-fold risk of hypertension , six-fold risk of diabetes and three-fold risk of dyslipidemia compared to autologous HSCT survivors.

- **Steroids** and calcineurin inhibitors including **cyclosporine** are used in post HSCT patients who present with high grade GVHD and cardiovascular risk factors such as **DM ,HTN and HLP** can develop as side effects of these agents.

- **Ruxolitinib**, an off-label treatment, has been added in steroid refractory GVHD and has known effect on **lipid profile** too.

GVHD and endothelial damage

- Arterial wall inflammation, lipid storage in endothelium and further vascular endothelial damage contribute to atherosclerosis.

- Loss of thrombomodulin, as a natural anticoagulant, is observed in biopsies of GVHD patients, too.

- In addition, endothelial damage leads to steroid resistance and failure of GVHD recovery.

	phatophysiology	presentation	Diagnostic tool
1.cardiomyopathy	-donor T cell infiltration -inflammatory cytokines (TNF,IL-2)	-ventricle systolic dysfunction -ventricle diastolic dysfunction -increased LV wall thickness and mass	-echocardiography
2.coronary artery disease	-traditional risk factors (HTN,DLP,DM) -arterial wall inflammation -endothelial dysfunction -loss of thrombomodulin	-coronary artery disease and pre mature atherosclerosis	-coronary angiography -ECG -cardiac troponin -echocardiography
3.arrhythmia	-Inflammatory cytokine(IL-2) -lymphocyte infiltration -drug	-tachyarrhythmia -bradicardia -complete heart block	-ECG -EPS
4.pericardial disease	-chronic inflammation of pericardium	-pericardial thickening -constrictive physiology	-Cardiac imaging(echocardiography ,CMR)

CARDIOMYOPATHIES

LV mass and wall thickness accompanied with **reduced E/A** in those
- s have developed chronic GVHD compared to non-GVHD group. however, LV diameter and LVEF have no significant difference in two groups.

- GVHD patients who receive immune suppressive agents such as **cyclosporine**, have significantly increased LV thickness and mass compared to patients did not.

Also post transplantation **cyclophosphamide** lead to reduce incidence of GVHD, although it is associated to **LV systolic dysfunction** and cardiac events within first 100 days after transplantation.

Coronary artery disease and Vascular thromboembolism

- **Traditional risk factors ,inflammatory responses and endothelial damage** can contribute to atherosclerosis in GVHD patients. **Atherosclerosis and CAD** are rare and life threatening late complications in these patients and can be observed **in young post HSCT** pts.

- **IMT** as an **early predictor** of atherosclerosis in GVHD patients and they reported higher IMT in ultrasonography of post BMT patients with chronic GVHD

- **Venous and arterial thromboembolism** is often associated to inflammation. **Endothelial dysfunction, decreased thrombomodulin-dependant generation of activated protein C** are implicated in GVHD pathogenesis and lead to procoagulant state

tachyarrhythmia, brady arrhythmia or Sinus node dysfunction and high degree atrioventricular block needs PPM

- **Lympho-histiocytic infiltration**, foci of **necrosis and scaring** in atrium and ventricle myocardium, atrioventricular node, bundle of His , right and left bundle branches were detected in patient's autopsy.

- Bradycardia associated GVHD often improve by increase immunosuppressive agents. A differential diagnosis for bradyarrhythmia in these pts is drug toxicity especially those received rapid infusion of high dose steroids pulse**. In fact, high dose of methyl prednisolone(>=4mg/kg/day) can cause lymphocytes death and an abrupt release of cytokines**. High serum concentration of **cyclosporine** is associated to bradyarrhythmia, too. **Ibrutinib** is used for treatment of chronic GVHD and is related to **atrial fibrillation**.

- Totally, in post HSCT patients who have developed GVHD and present with unexplained dysrhythmia or coronary arteries disease ,cardiac GVHD should be considered.

Constrictive pericarditis

- **Constrictive pericarditis** associated to GVHD is a rare but potentially reversible condition . It has been resolved by systemic immunosuppressive therapy in early stage of disease and before permanent pericardium thickening. Although, Surgical partial pericardectomy and immunomodulatory therapy with ruxolitinib were performed for patient with CP.

Cardiovascular diseases in patients after hematopoietic stem cell transplantation: Systematic review and Meta-analysis - 03/02/23

Doi : 10.1016/j.retram.2022.103363

Azin Alizadehasl [a], Nashmil Ghadimi [a], Hossein Hosseinifard [b], Kamran Roudini [c], Amir Hossein Emami [d], Ardeshir Ghavamzadeh [e], Davood khoda-Amorzideh [a, *]

Vol 71 – N° 1
Article 103363- janvier 2023
Retour au numéro

CVDs in post HSCT patients	prevalence
CVD	16.84%
PE	19.72%
arrhythmia	3.91%
CHF	3.66%
stroke	0.22%
CAD	1.36%
death	1.53%

- **ONLY ONE NUMBER (LVEF) CANNOT CANCEL THE HSCT**

Published in final edited form as:
Biol Blood Marrow Transplant. 2015 February ; 21(2): 300–304. doi:10.1016/j.bbmt.2014.10.011.

Hematopoietic Stem Cell Transplantation in Patients with Systolic Dysfunction: Can It Be Done?

Peter Hurley[1,*], **Suma Konety**[2], **Qing Cao**[3], **Daniel Weisdorf**[1], and **Anne Blaes**[1]

[1] Division of Hematology Oncology and Transplantation, Department of Medicine, University of Minnesota, Minneapolis, Minnesota

[2] Division of Cardiovascular Diseases, University of Minnesota, Minneapolis, Minnesota

[3] Biostatistic Core, Masonic Cancer Center, University of Minnesota, Minneapolis, Minnesota

- **Our study demonstrates that patients with asymptomatic borderline systolic dysfunction can safely undergo HCT with RIC. Coronary artery disease remains a risk factor for increased TRM. Patients with borderline systolic dysfunction can safely undergo HCT, but may need particular vigilance for potential hemodynamic or ischemic cardiac complications.**

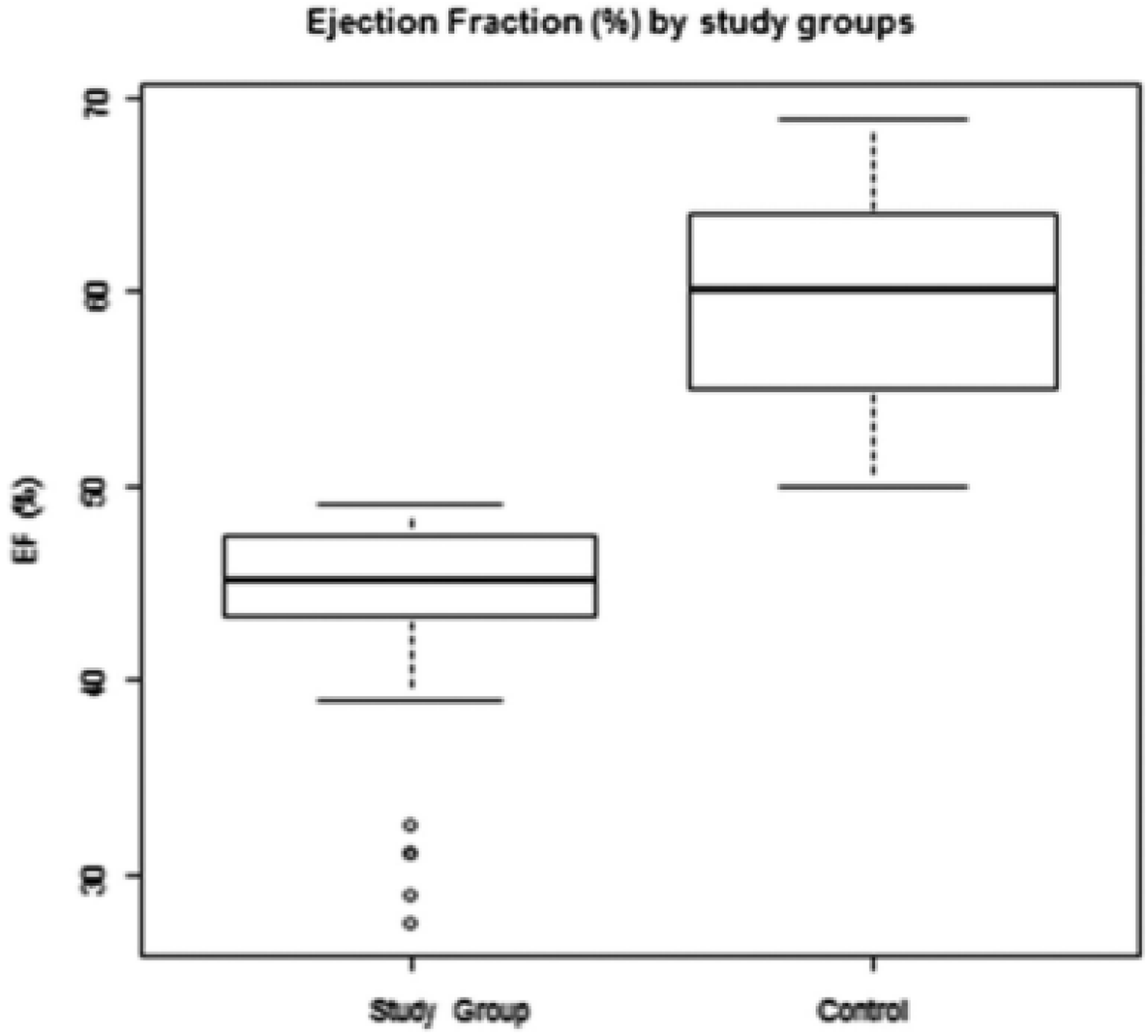


Figure 1.
Box plot comparing the range of ejection fractions of the 2 groups.

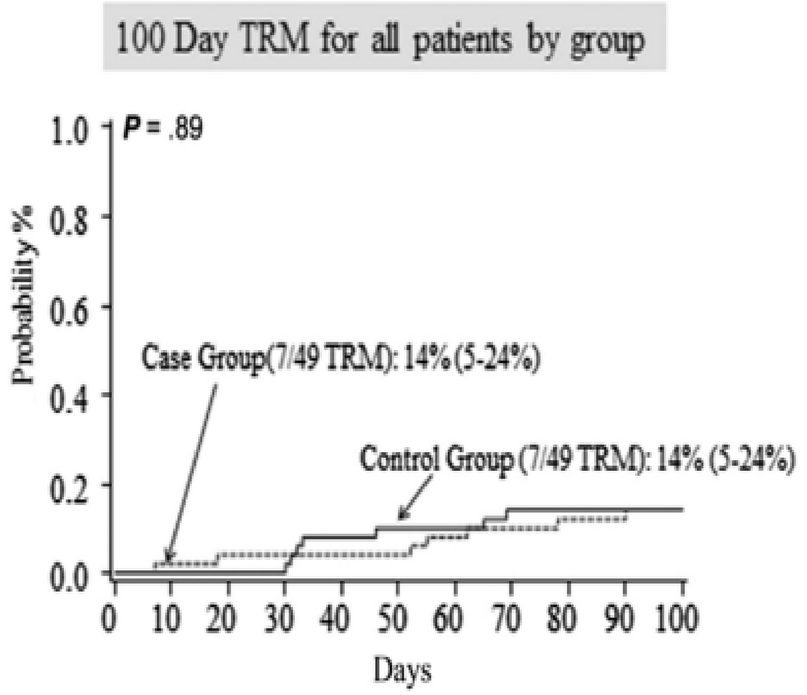


Figure 2.
TRM was identical between the study and control groups at 100 days.

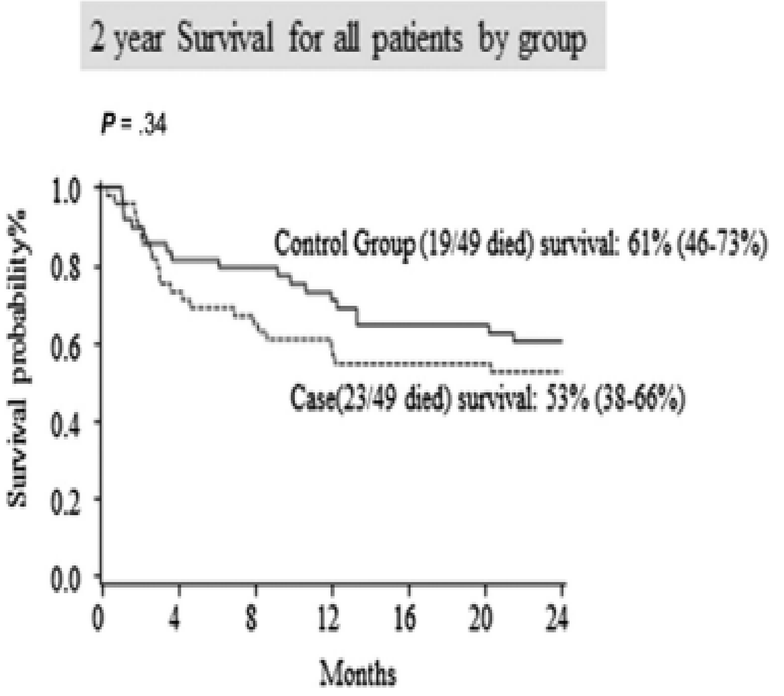


Figure 3.
Kaplan-Meier curves show similar survival between the study and control groups.

Our study demonstrates that **patients with asymptomatic borderline systolic dysfunction can safely undergo HCT with RIC**. Coronary artery disease remains a risk factor for increased TRM.

Mehr 24, 1393 AP

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ISSUES FIRST EDITION ABSTRACTS COLLECTIONS

TRANSPLANTATION | NOVEMBER 1, 2007

Premature cardiovascular disease after allogeneic hematopoietic stem-cell transplantation

André Tichelli, Christoph Bucher, Alicia Rovó, Georg Stussi, Martin Stern, Michael Paulussen, Jörg Halter, Sandrine Meyer-Monard, Dominik Heim, Dimitrios A. Tsakiris, Barbara Biedermann, Jakob R. Passweg, Alois Gratwohl

Blood (2007) 110 (9): 3463–3471.

https://doi.org/10.1182/blood-2006-10-054080

Article history

in multivariate analysis, allogeneic HSCT (RR: 1.16, P = .1003), and at least 2 of 4 cardiovascular risk factors (hypertension, dyslipidemia, diabetes, obesity) (RR: 12.4; P =.02) were associated with a higher incidence of arterial events after HSCT. Thus, long-term survivors after allogeneic HSCT are at high risk for premature arterial vascular disease. HSCT might favor the emergence of established risk factors, such as hypertension, diabetes, and dyslipidemia.

Open access Heart failure and cardiomyopathies

openheart

Impaired right ventricular function in long-term survivors of allogeneic haematopoietic stem-cell transplantation

Richard John Massey ,[1,2] Phoi Phoi Diep,[2,3,4] Marta Maria Burman,[2,3,4] Anette Borger Kvaslerud ,[1,2] Lorentz Brinch,[4] Svend Aakhus,[5,6] Lars Gullestad ,[1,2,7] Ellen Ruud ,[2,8] Jan Otto Beitnes[1]

Studies of treatments during HSCT to prevent both acute and late CV toxicity are limited

- **ACE-I and beta-blockers are effective**

- **Outpatient and home-based exercise after HSCT can improve exercise capacity and quality of life**

JACC: CARDIOONCOLOGY VOL. 2, NO. 3, 2020

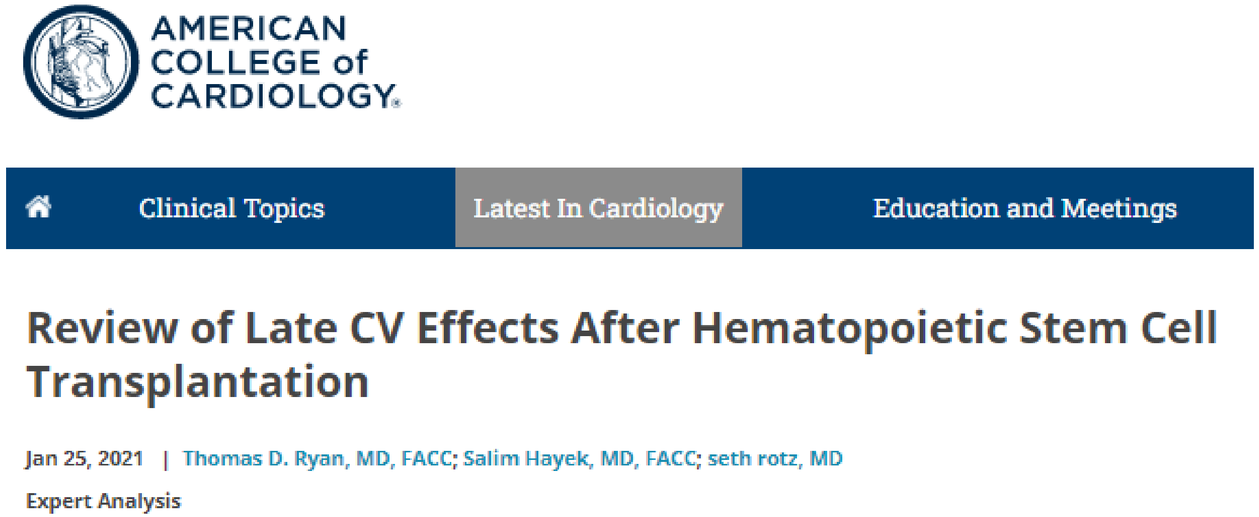
ORIGINAL RESEARCH

Left Ventricular Systolic Function in Long-Term Survivors of Allogeneic Hematopoietic Stem Cell Transplantation

Richard J. Massey, MSc,[a,b] Phoi P. Diep, MD,[b,c,d] Ellen Ruud, MD, PhD,[b,c] Marta M. Burman, MD,[b,c,d] Anette B. Kvaslerud, MD,[a,b] Lorentz Brinch, MD, PhD,[e] Svend Aakhus, MD, PhD,[f,g] Lars L. Gullestad, MD, PhD,[a,b,h] Jan O. Beitnes, MD, PhD[a]

- Clinical factors independently associated with 2D-LVEF and/or GLS included age, anthracyclines, graft versus host disease (GVHD), **heart rate, and hypertension**. In the 45% of survivors pre-treated with anthracyclines, the effect of anthracyclines on 2D-LVEF and GLS was dose-dependent.

AMERICAN COLLEGE of CARDIOLOGY

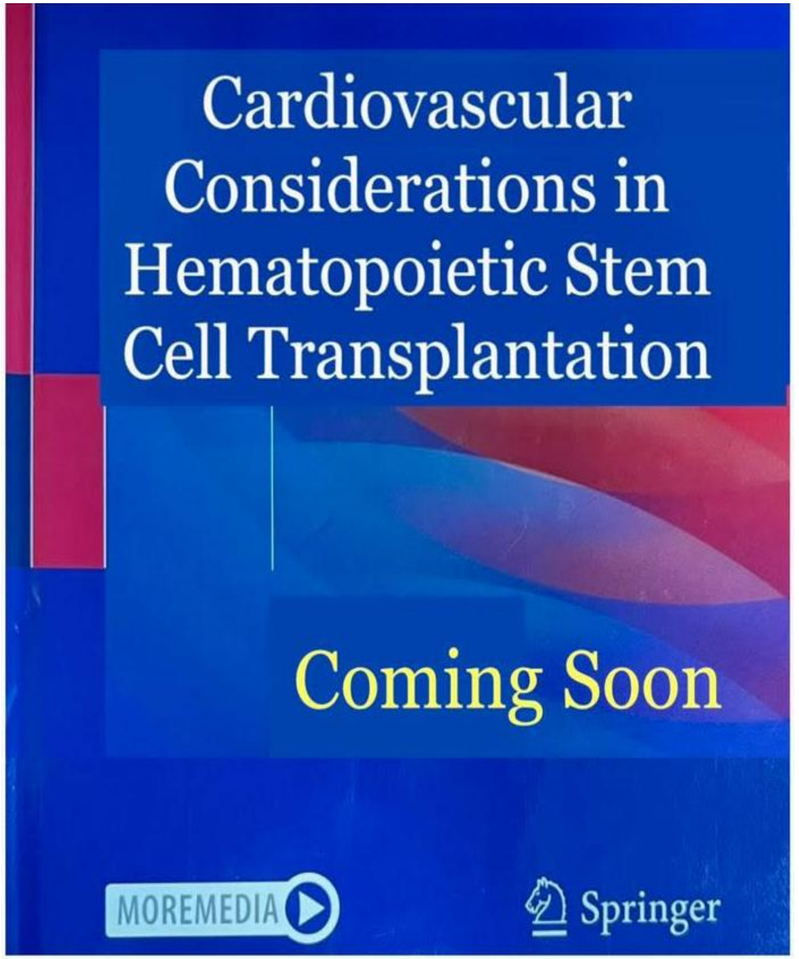


- **Collaborations between hematologists and cardio-Oncologists are crucial in limiting toxicity during HSCT and managing late complications.**

ONLY ONE NUMBER (LVEF) CANNOT CANCEL THE HSCT

Cardio-Oncology Department and Research Center
Rajaie Cardiovascular Medical & Research Center, Tehran, Iran

Thank you
for your attention



Several questions must be answered in the coming years to improve outcomes

- Can biomarkers be used repeatedly over weeks to months as a guide to tapering immunosuppression?
- Which patients need different modes of supportive care (eg, remediation of dysbiosis vs tissue damage), and can this even be distinguished biologically?
- How long should adjunct repair- based therapies such as uhCG/EGF be continued to achieve maximal mucosal healing?
- What other targets of aGVHD (eg, the endothelium) should be treated?
- Additional clinical trials are urgently needed to address these questions.
- What do perform standardizing data reporting
- Question: over suppression of aGVHD may be facilitate cGVHD??Relapse/Graft Failure