Lo scambio plasmatico e le strategie di desensibilizzazione dei riceventi con DSA

Mattia Algeri

IRCCS Ospedale Pediatrico Bambino Gesù, Roma

Bologna, 04 ottobre 2023

XLVIII CONGRESSO NAZIONALE AIEOP

Bologna
2-4 Ottobre 2023

Il sottoscritto Mattia Algeri.

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

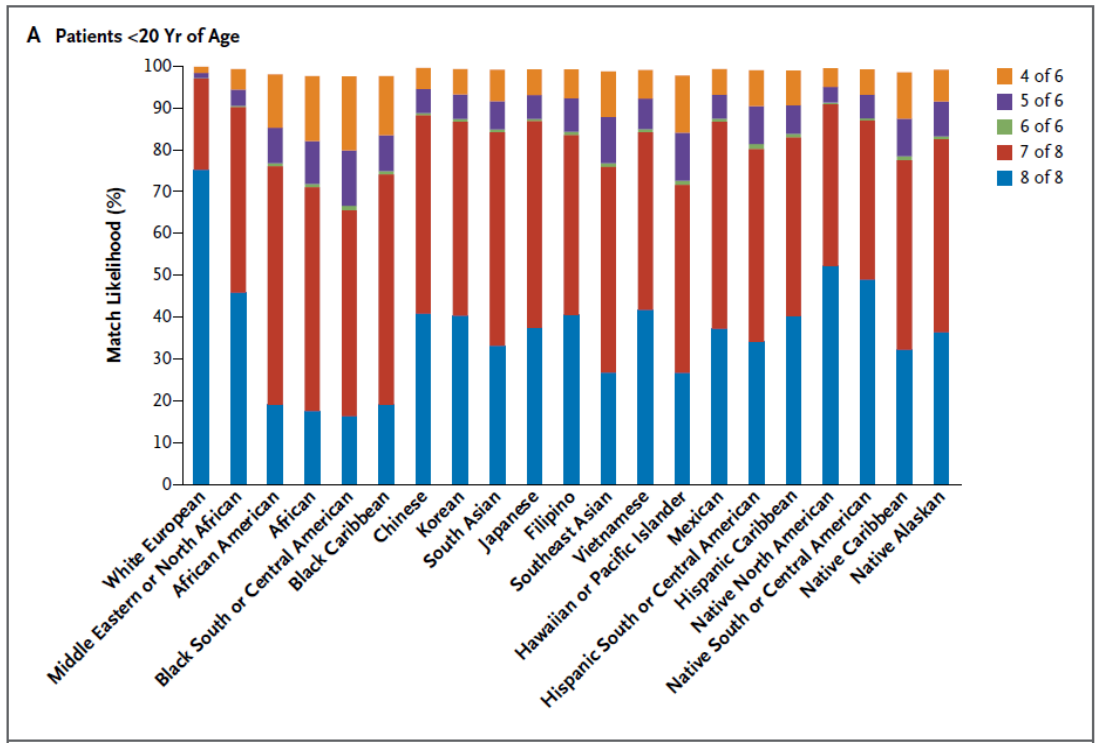
dichiara

- ❑ *che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:*
  - ***Vertex Pharmaceuticals:*** *membro di advsisory board e steering committee*

Probability to find an HLA-matched donor

SPECIAL ARTICLE

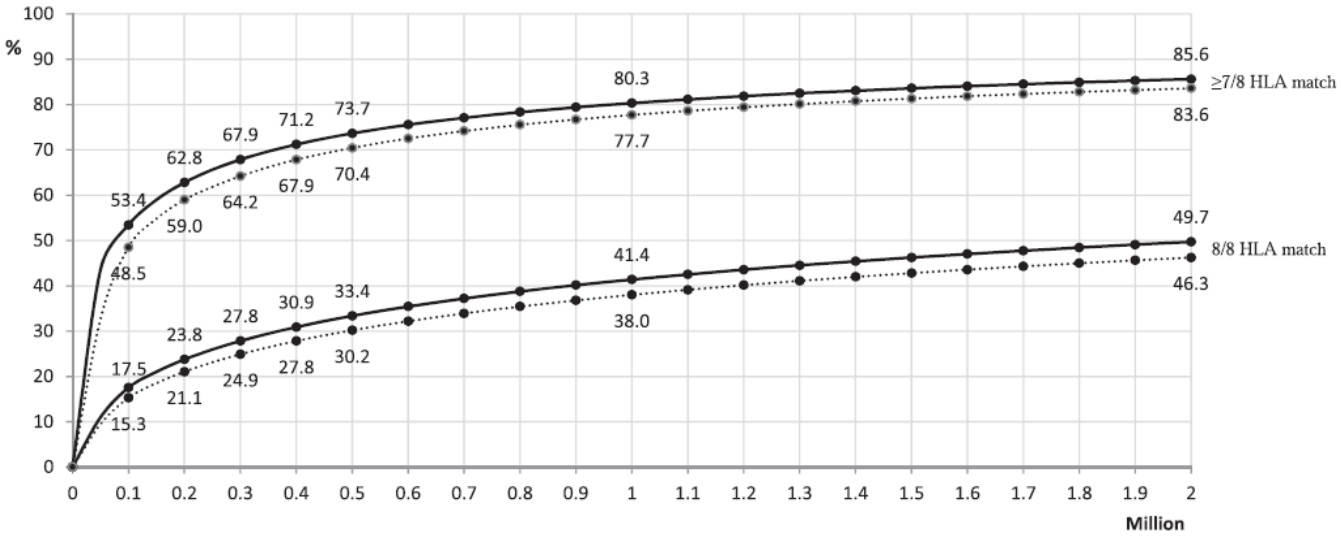
HLA Match Likelihoods for Hematopoietic Stem-Cell Grafts in the U.S. Registry



Gragert *et al.*, NEJM 2014

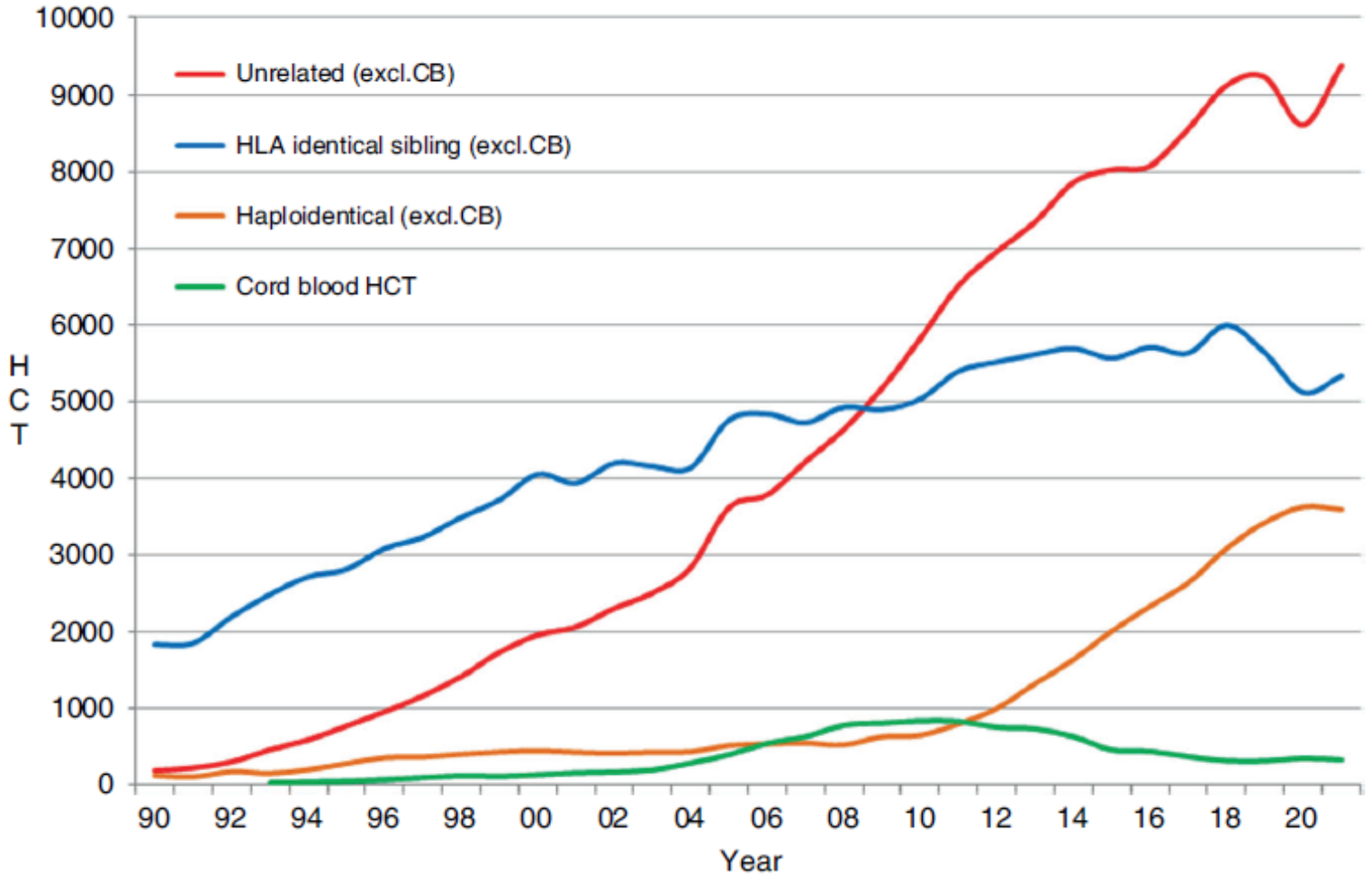
Availability of HLA-allele-matched unrelated donors and registry size: Estimation from haplotype frequency in the Italian population

N. Sacchi [a,*], F. Ciceri [b], F. Bonifazi [c], M. Algeri [d], A. Gallina [a], S. Pollichieni [a], E. Raggio [a], B. Hadj-Amar [e], L. Lombardini [f], S. Pupella [g], G. Liumbruno [g], M. Cardillo [f]



N. Sacchi, et al. Hum Immunol 2021

Increased use of alternative donors

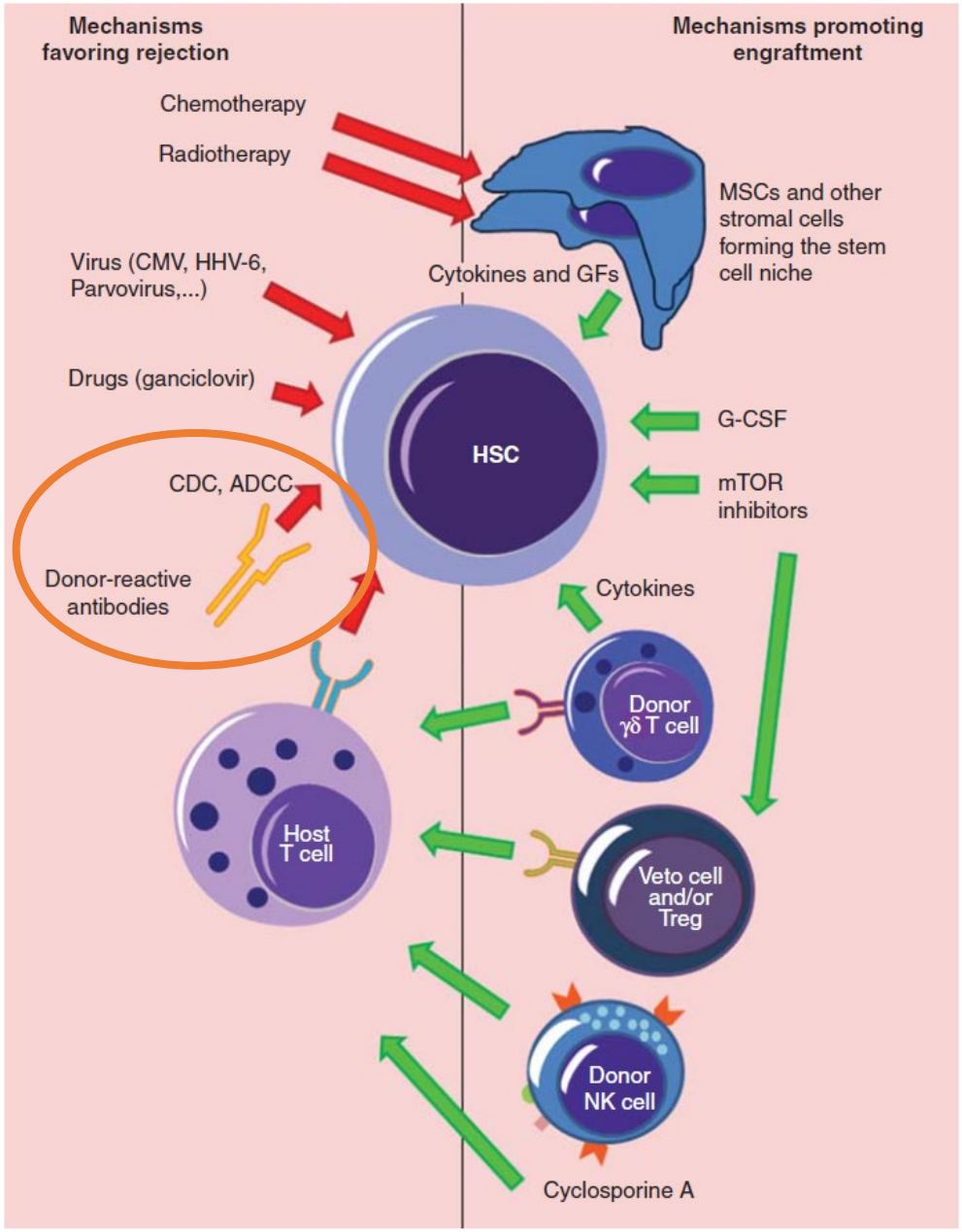


J.E. Passweg et al, BMT 2023

Risk of GRAFT FAILURE after haploidentical HSCT: 9-30%[1,2]

[1] S.O. Ciurea et al, BBMT 2015. [2] P. Merli et al.. Blood Adv 2022.

Graft failure



RISK FACTORS

- HLA mismatches
- Nonmalignant disease (↑↑ SAA, Haemoglobinopathies)
- Advanced disease
- Graft source (UCB)
- Conditioning (NMA/RIC)
- T-cell depletion
- Anti-HLA antibodies
- Extensive marrow fibrosis extensive prior treatment
- Donor age
- ABO mismatch
- Splenomegaly
- Cell dose
- Viral infections
- GVHD
- Drug toxicity
- Iron overload
- Transfusion history

F. Locatelli et al, Expert Opin Pharmacother. 2014
D. Valcárcel and A. Sureda, EBMT Handbook 2019

Donor Specific Antibodies (DSA)

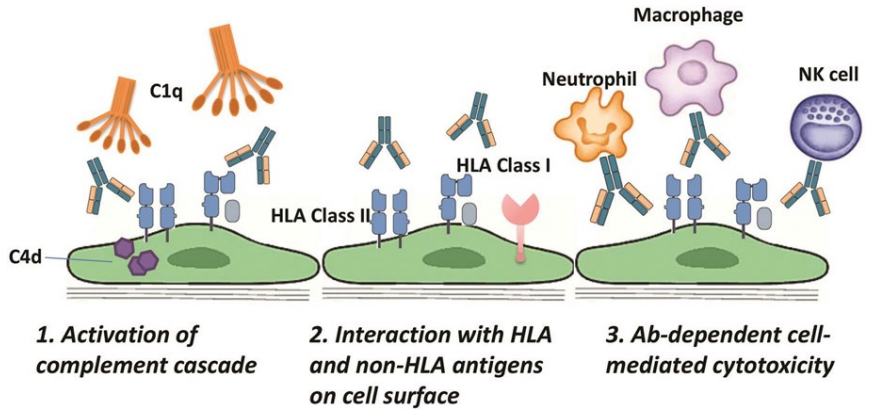
Preformed antibodies in the recipient directed against the candidate donor's class I and/or class II HLA antigens

Formation of antibodies to allogeneic HLA antigens after exposure to foreign cells or tissue through:

- *Pregnancy*
  - -Result of sensitization during pregnancies by offspring's HLA antigens
  - -Risk with a higher number of pregnancies (reported incidence up to 50% in the female recipient with a history of multiple pregnancies)[1]
- *Blood product transfusion*[2]
- *Previous transplantation*[3]

Rate of HLA sensitization in HSCT candidates: 20% to 40%[3-7]

Rate of DSA to at least one potential donor: 1.4% to 24%[3-7]



Hematopoietic Stem Cell Transplantation (Graft Failure, Poor Graft Function, Delayed Engraftment)

Tranfusion medicine (Tranfusion refractoriness, TRALI)

Solid Organ Transplantation (Hyperacute, acute, chronic rejection)

[1] L. Morin-Papunen L et al, Med Biol 1984. [2] M.D. Seftel et al, Blood 2004. [3] S. Yoshihara et al, Bone Marrow Transplant 2012. [4] Y.-J. Chang, et al, J. Hematol. Oncol 2015. [5] S. Spellman et al. Blood 2010. [6] H. Yamamoto et al, Biol. Blood Marrow Transplant 2014. [7] D.E. Gladstone et al, Biol. Blood Marrow Transplant 2013.

First description of the role of DSA in HSCT

The New England
Journal of Medicine

Volume 320 JANUARY 26, 1989 Number 4

EFFECT OF HLA COMPATIBILITY ON ENGRAFTMENT OF BONE MARROW TRANSPLANTS IN PATIENTS WITH LEUKEMIA OR LYMPHOMA

CLAUDIO ANASETTI, M.D., DEBORAH AMOS, PATRICK G. BEATTY, M.D., PH.D., FREDERICK R. APPELBAUM, M.D., WILLIAM BENSINGER, M.D., C. DEAN BUCKNER, M.D., REGINALD CLIFT, KRISTINE DONEY, M.D., PAUL J. MARTIN, M.D., ERIC MICKELSON, BRENDA NISPEROS, JOHN O'QUIGLEY, PH.D., ROBERT RAMBERG, JEAN E. SANDERS, M.D., PATRICIA STEWART, M.D., RAINER STORB, M.D., KEITH M. SULLIVAN, M.D., ROBERT P. WITHERSPOON, M.D., E. DONNALL THOMAS, M.D., AND JOHN A. HANSEN, M.D.

Positive crossmatch for anti-donor lymphocytotoxic antibody determined a significant risk for primary graft failure

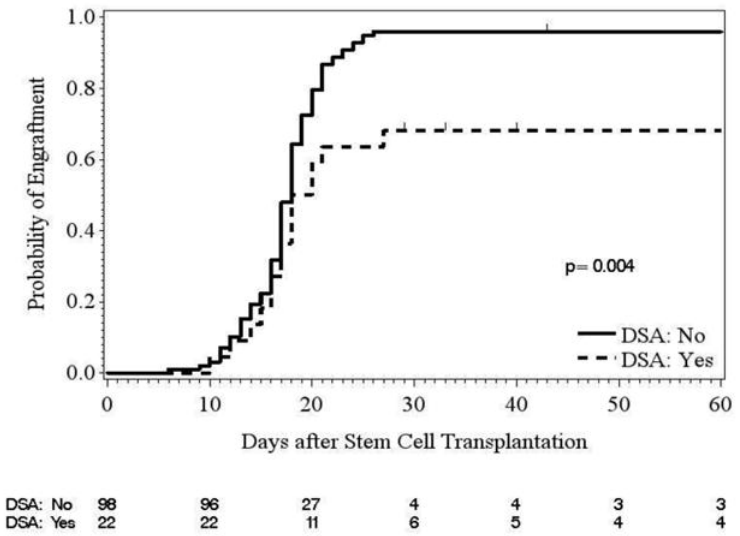
Relative risk = 2.3; P = 0.0038

DSA impact in different allogeneic HSCT settings

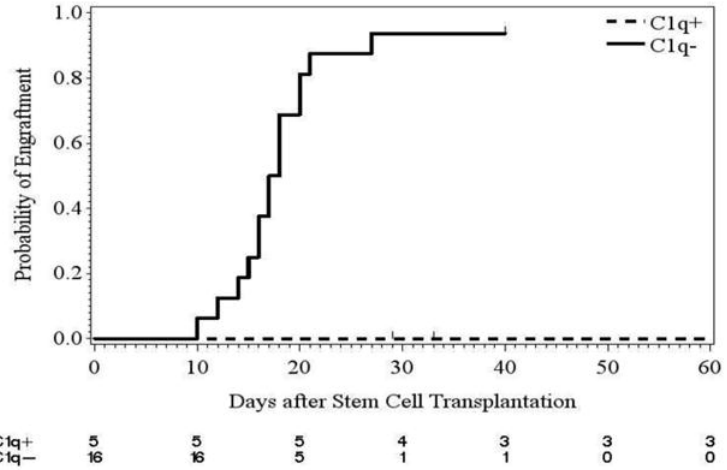
	Patients (*n*)	Stem cell source	Conditioning	Anti-HLA%	DSA%	Graft failure with/without DSA
Spellman et al. *Blood* 2010	115	Mismatched unrelated	RIC	ND	9	24 versus 1%
Ciurea et al. *Blood* 2011	592	10/10 and 9/10 unrelated	MAC or RIC	19.6	1.4	37.5 versus 2.7%
Ciurea et al. *Blood* 2011	24	Haplo-identical	RIC	ND	21	60 versus 5%
Yoshihara et al. *BMT* 2021	79	Haplo-identical	RIC	20.2	14	27 versus 3%
Chang et al. *J Hematol Oncol* 2015	345	Haplo-identical	MAC	25.2	11.3	61% (MFI>10,000) versus 3.2%
Ciurea et al. *BBMT 2015*	122	Haplo-identical	Non-specified	ND	18	32 versus 4%
Takanashi et al. *Blood* 2010	386	Single CBU	MAC	23.1	5	83 versus 32%
Cutler et al. *Blood* 2011	73	Double CBU	MAC or RIC	ND	24	57 versus 5.5%
Ruggeri et al. *Haematologica* 2013	294	Single and double CBU	RIC	23	5	81 versus 44%
Yamamoto et al. *BBMT 2014*	175	Single CBU	MAC or RIC	39.4	ND	50% if anti-HLA-C, DP, DQ, DRB1/2/3 versus 16%

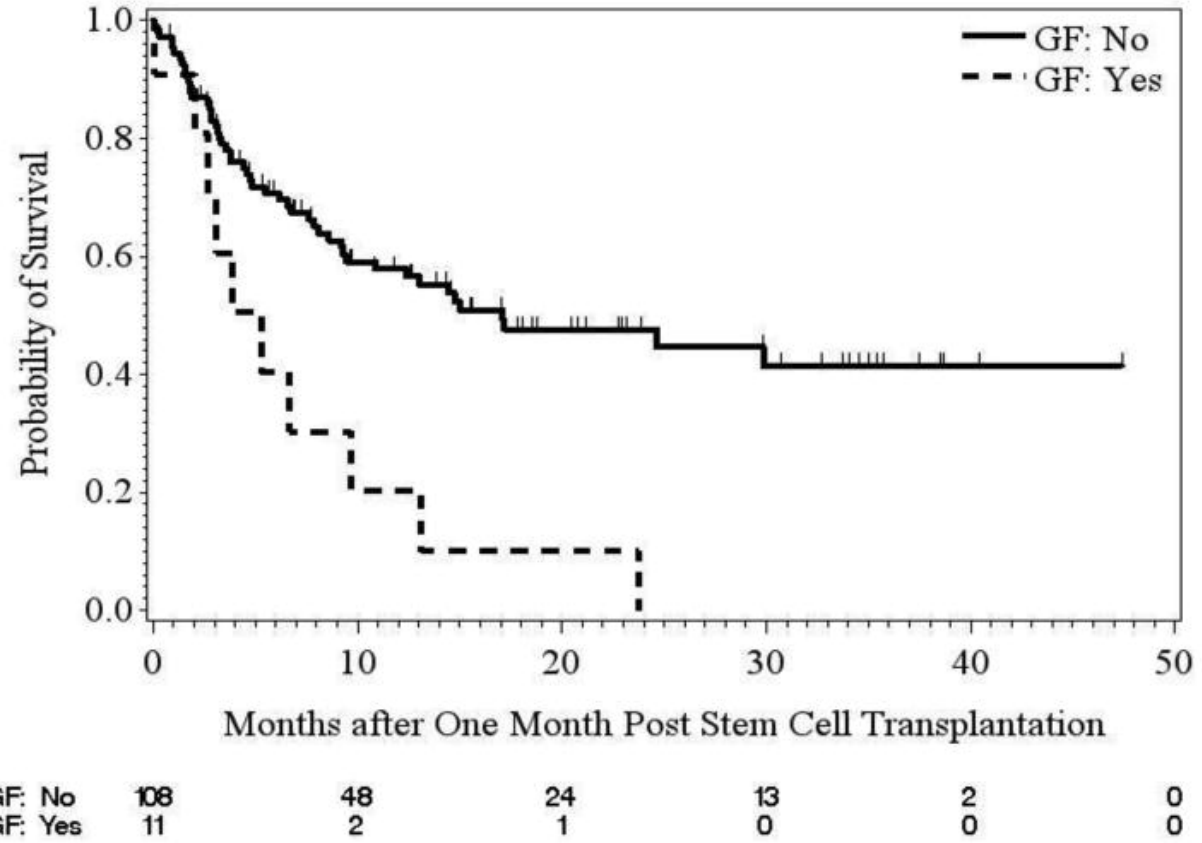
DSA are associated with a higher incidence of GF and poor survival

A.



B.

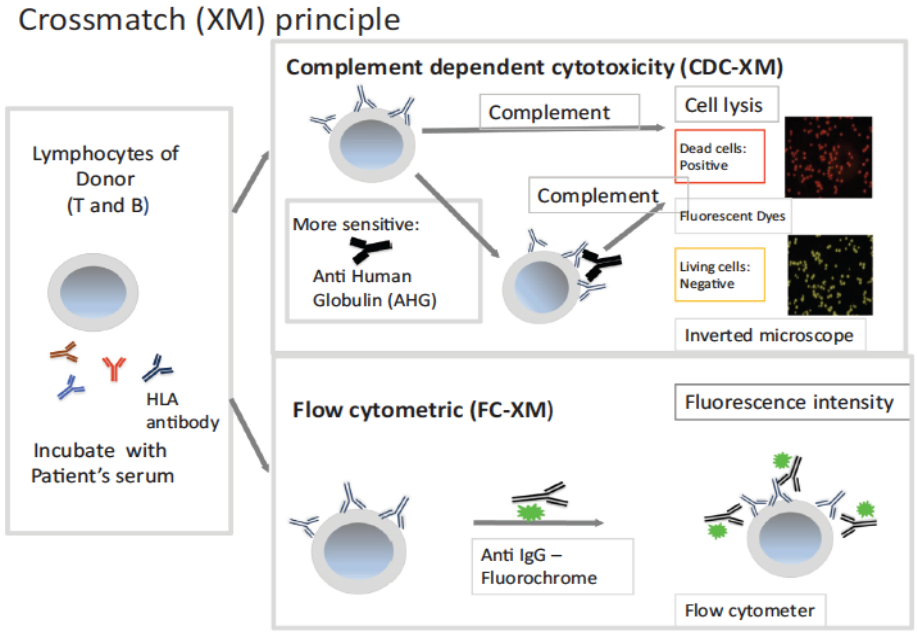




S.O. Ciurea et al, BBMT 2015

DSA identification assays

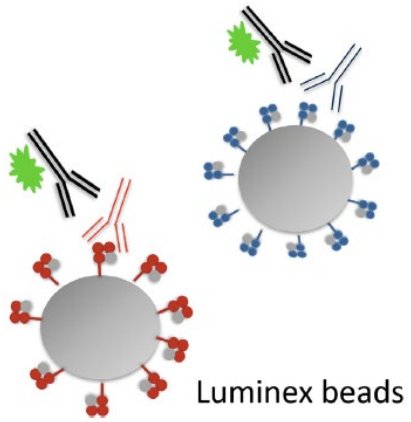
- **Cell-based:** require donor lymphocytes



- ✓ "Functional" test
- ✗ Low sensitivity

- ✓ Higher sensitivity
- ✗ Do not distinguish therapeutic antibodies (e.g. rituximab)

- **Solid-phase assays**: do NOT require donor lymphocytes



- ✓ High specificity and sensitivity
- ✓ Semiquantitative (MFI)>>>Virtual crossmatch
- ✓ Precise detection of anti-HLA antibodies
- ✗ Possible false positive or antibody levels underestimation
- ✗ No info about antibody functionality
- ✗ Not completely quantitative (MFI values do not translate directly into the antibody level)

- C1q assay ✓ distinguish complement fixing from non-complement fixing antibodies

M.P. Bettinotti, Human immunology 2022

Donor Specific Antibodies (DSA)

Highest relevance in partially HLA-mismatched allogeneic hematopoietic stem cell transplantation (multiple class I and II mismatches)[1]

Donor type	HLA loci								
HLA identical sibling	A	C	B	DRB1	DRB3/4/5	DQA1	DQB1	DPA1	DPB1
	A	C	B	DRB1	DRB3/4/5	DQA1	DQB1	DPA1	DPB1
Haploidentical related	A	C	B	DRB1	DRB3/4/5	DQA1	DQB1	DPA1	DPB1
	A	C	B	DRB1	DRB3/4/5	DQA1	DQB1	DPA1	DPB1
MUD 8/8	A	C	B	DRB1	DRB3/4/5	DQA1	DQB1	DPA1	DPB1
	A	C	B	DRB1	DRB3/4/5	DQA1	DQB1	DPA1	DPB1
MUD 10/10	A	C	B	DRB1	DRB3/4/5	DQA1	DQB1	DPA1	DPB1
	A	C	B	DRB1	DRB3/4/5	DQA1	DQB1	DPA1	DPB1
MUD 12/12	A	C	B	DRB1	DRB3/4/5	DQA1	DQB1	DPA1	DPB1
	A	C	B	DRB1	DRB3/4/5	DQA1	DQB1	DPA1	DPB1
CBU 6/6	A	C	B	DRB1	DRB3/4/5	DQA1	DQB1	DPA1	DPB1
	A	C	B	DRB1	DRB3/4/5	DQA1	DQB1	DPA1	DPB1

Classic “10 out of 10” HLA-matched alloBMTs: HLA-A, -B, -C, DRB1, and DQB1

HLA-DPB1, DRB3, DRB4, and DRB5 are not necessarily matched

Mismatching amenable to DSA formation occurs in more than half of the “10 out of 10” HLA-matched unrelated donor alloBMTs[2]

HLA antibodies are dynamic!

After inflammatory events, such as infection or tissue trauma, reactivation of dormant HLA-specific memory B cells may result in the production of DSAs without re-exposure to foreign tissue.[3]

Importance of HLA antibody reassessment over time.

[1] S.O. Ciurea et al, BMT 2018. [2] B.E. Shaw et al, Leukemia. 2010. [3] J.E. Locke et al, Am J Transplant. 2009.

Desensitization strategies

Strategy	Method
Antibody removal	Plasma exchange (PE/TPE, Plasmapheresis)
	Immunoadsorption
Antibody neutralization **Enhanced clearance of anti-HLA antibodies**	Intravenous immunoglobulin
	Donor platelets or “buffy coat” (white blood cells) infusion
Inhibition of antibody production	Anti-CD20+ B cells monoclonal antibody: rituximab
	Proteazome inhibition: bortezomib
	Splenectomy*
Complement cascade blockage	Anti-C5a: Eculizumab*
	Intravenous immunoglobulin

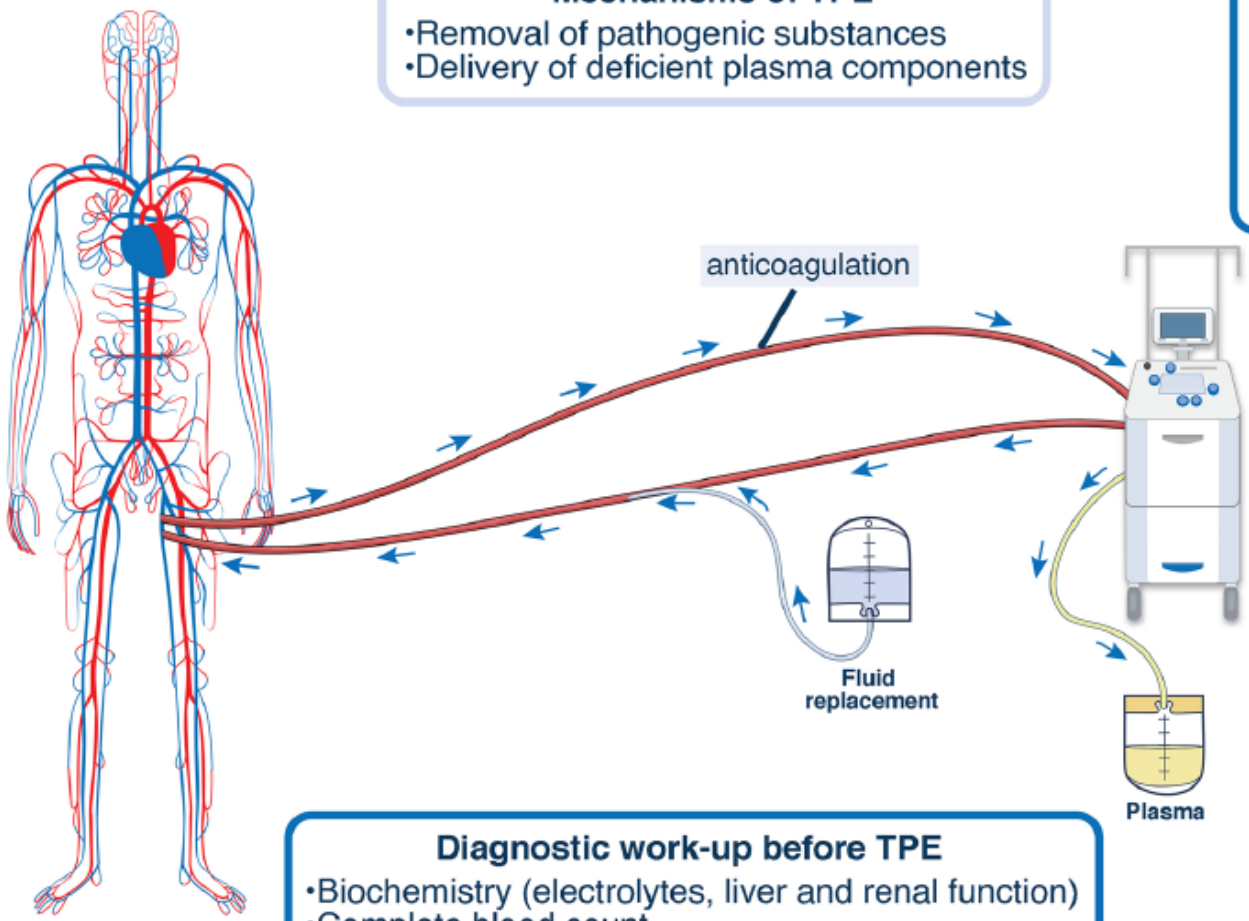
*Not used in hematopoietic stem cell transplantation to date

Most of the published data regarding transplant outcomes in allogeneic HSCT patients receiving these desensitization methods are case reports or small studies with limited number of patients and variety of graft outcome

Plasma exchange: overview

Mechanisms of TPE
- Removal of pathogenic substances
- Delivery of deficient plasma components

Prescription of TPE
- Vascular access
- Total plasma volume
- Number of sessions
- Interval between sessions
- Anticoagulation
- Type of replacement fluid
- Drug dosing



Diagnostic work-up before TPE
- Biochemistry (electrolytes, liver and renal function)
- Complete blood count
- Coagulation
- Disease-specific tests
- Infection status (HIV, hepatitis..)
- Blood type (ABO, Rhesus)

Monitoring during TPE
- Biochemistry
- Complete blood count
- Coagulation
- Disease-specific tests

P.R. Bauer et al, Intensive Care Med 2022

First report of desensitization with plasma exchange for allogeneic HSCT

MORE RECENT PROTOCOLS:
Plasma exchange combined with other methods, which aim to inhibit antibody production and antibody neutralization.

Bortezomib
In renal transplant recipients, bortezomib was shown to transiently eliminate DSA in 69% of patients with a median time to reemergence of DSA of 3.8 months.
In the case of SCT, transient suppression of DSA production may be sufficient as plasma cells will eventually be donor derived.

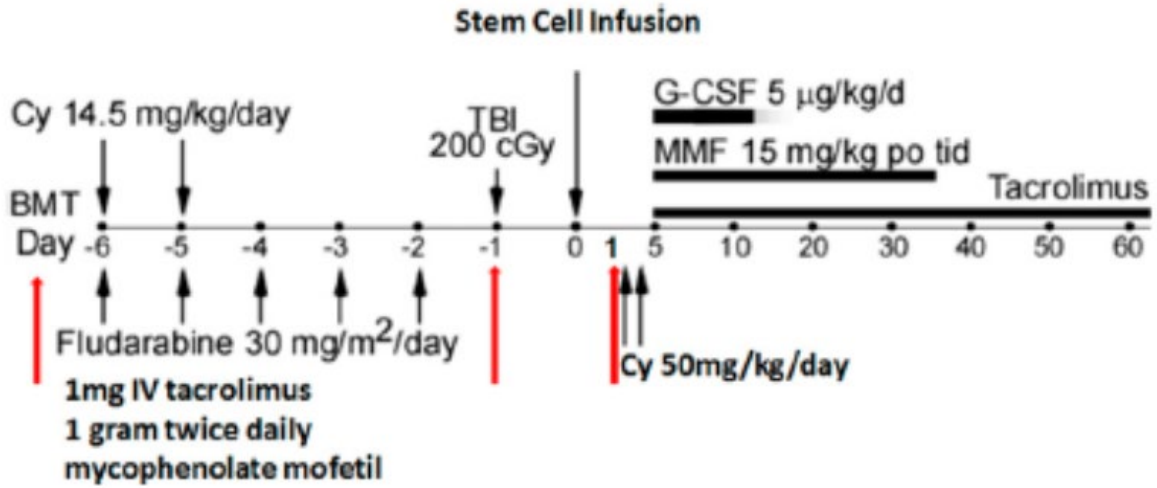
Rituximab
DSA abrogating effect similar to Bortezomib.
This effect is typically more delayed then bortezomib and takes up to 3 months.

I.v. Ig
Decreases the half-life of IgG Abs by facilitating their endocytotic degradation in the endothelial cells and enhancing their clearance from the serum

Desensitization integrated into conditioning regimen

Donor HLA-specific Abs: to BMT or not to BMT?

MS Leffell[1], RJ Jones[2] and DE Gladstone[2]



The desensitization process, integrated into the RIC regimen, starts 1 to 2 weeks before conditioning:

- Alternate-day, single plasma volume TPE (↑) with post-TPE/IVIg (0.1 g/kg),
- Tacrolimus (1 mg IV/d), continued through day 21.
- Mycophenolate mofetil (1 g twice daily), continued through day 21.
- 1 TPE/IVIg treatment on day -1

On day -7 of desensitization, DSA levels are repeated to ensure a MFI reduction suggestive of a negative FCXM before conditioning commencement.

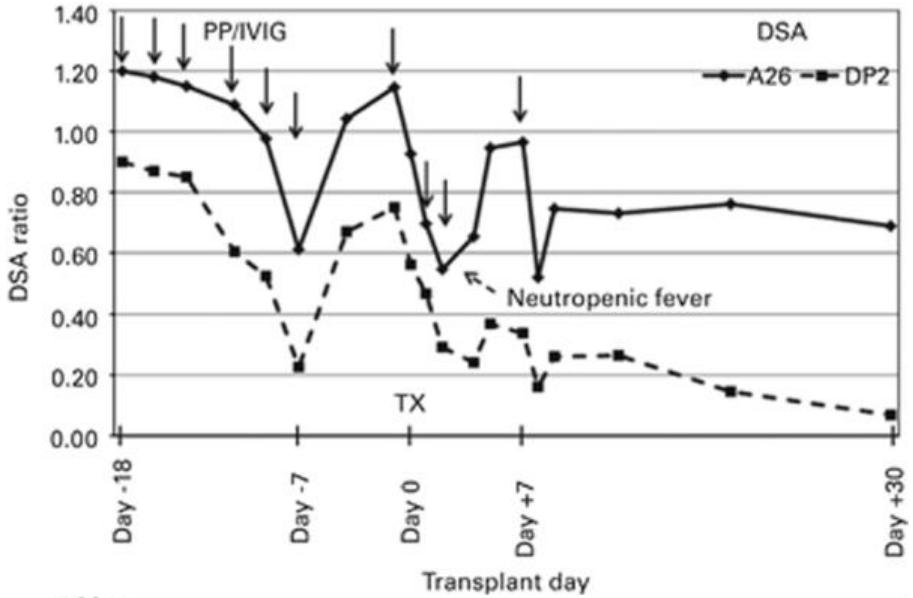
Number of preconditioning TPE/IVIg treatments based on starting DSA levels correlated to crossmatch tests.

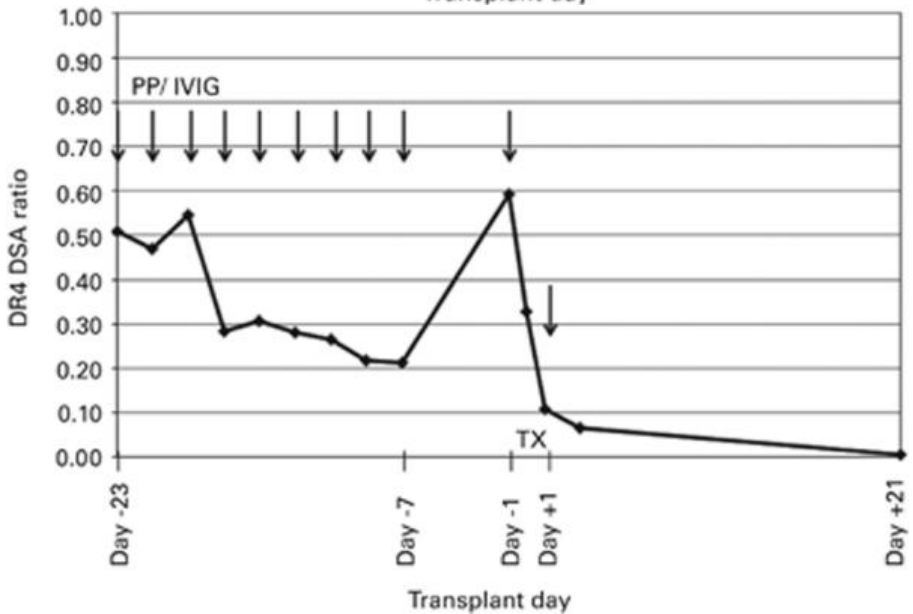
- DSAs at a level of weak to moderately positive FCXM: **3-4.**
- Strongly positive FCXM, crossmatch due to the presence of class II antibodies (less amenable to reduction), multiple DSAs, HLA mismatches repeated from a previous transplant, a child-to-mother transplant, increasing DSA level before the initiation of treatment: **5-6**

Additional DSA measurement is made on day -1.
In case of DSA rebound 1 to 2 additional TPE/IVIg treatments are prescribed on day +1 and potentially on day +2.
Additional monitoring is performed on days +3 and +5 to determine if additional post-BMT treatments are needed.

M.S. Leffel et al, BMT 2015

Desensitization integrated into conditioning regimen





Pt. no.	Disease	Donor chimerism day +60 % donor		GVHD	Disease relapse	F/U time
		Unsorted PBL	CD3+ PBL			
1	AML	100	100	No	No	3.9 Years
2	AML	94	NT	No	3 Mos.	Died: 17 mos.
3	AML	>95	100	No	5 Mos.	Died: 7 mos.
4	MDS	100	100	Grade 1 skin	No	Died: 2.3 years viral pneumonia
5	MDS	100	100	Grade 1 skin	12 Mos.	Died: 18 mos.
6	MDS	100	100	No	16 mos.	Died: 20 mos.
8	T-cell lymphoma	100	100	Grade 1 skin	No	Died: 1.1 years hepatitis C
9	Hodgkin's lymphoma	>95	<5	No	No	2.1 Years
10	AML	>95	100	No	4 Mos.	Died
11	MDS	>95	100	No	No	Died non-transplant related
12	SS	94	<5	No	No	1.5 Years
13	AML	>95	100	No	4 Mos.	Died: 4.3 mos.
14	AML	100	<5	No	No	1 Year
15	AML	100	100	Grade 1 skin	4 Mos.	Died: 4 mos.

DSA reduced to levels considered negative post-transplant in 11 patients
DSA remained at low levels in 3 patients
All 14 patients achieved donor engraftment by Day +60
7 patients relapsed (too immunosuppressive?)

M.S. Leffel et al, BMT 2015

DSA rebound

CASE REPORT

TRANSFUSION

Rebound and overshoot of donor-specific antibodies to human leukocyte antigens (HLA) during desensitization with plasma exchanges in hematopoietic progenitor cell transplantation: A case report

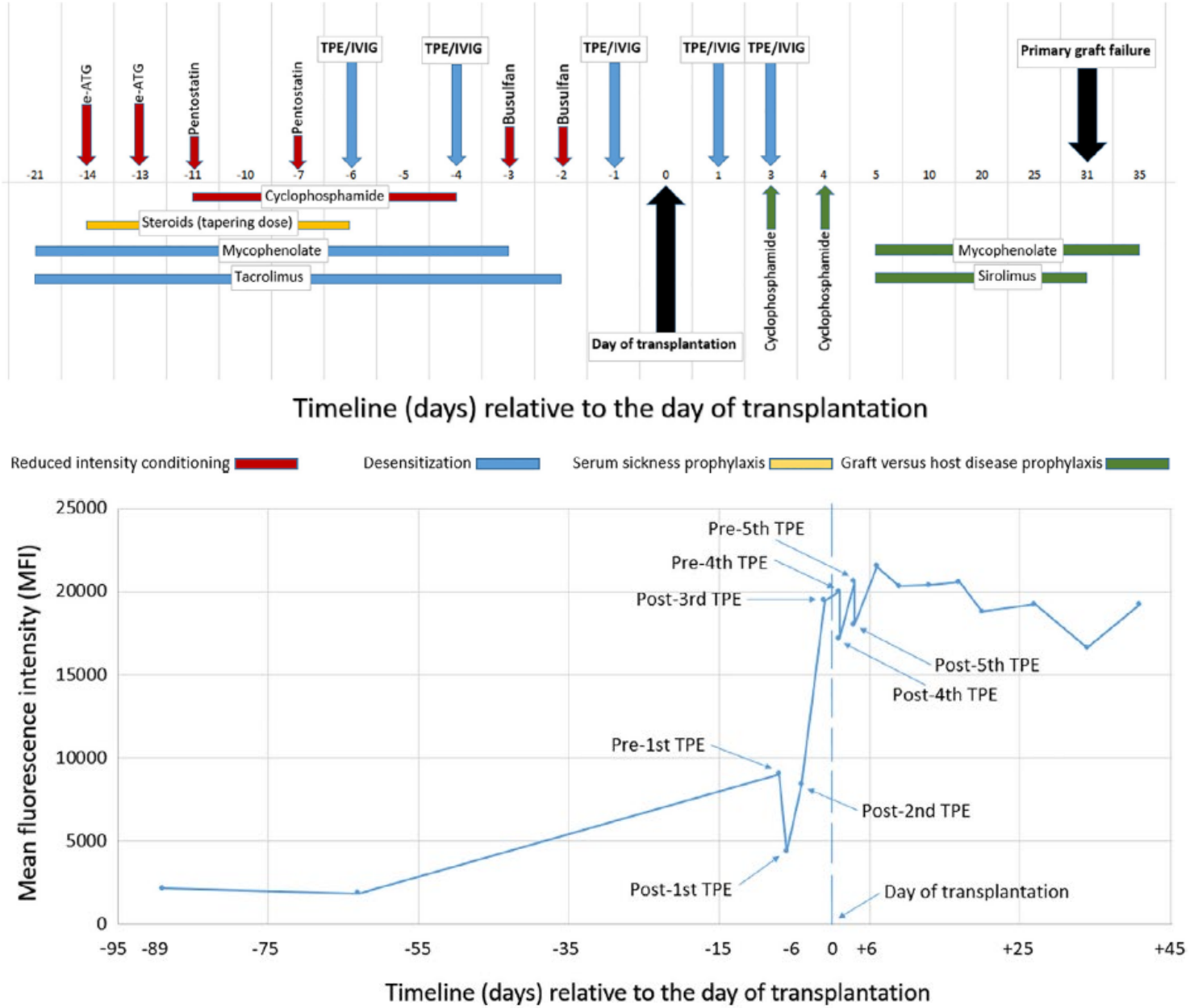
Sajjad Hassan[1] | Kamille A. West[1] | William W. Ward[1] | Jennifer A. Kanakry[2] | Willy A. Flegel[1]

Abstract

Background: Donor-specific antibodies (DSA) to HLA have been associated with graft loss in hematopoietic progenitor cell (HPC) transplantation. Limited data associate therapeutic plasma exchange (TPE) with desensitization and successful engraftment. We report an attempt of desensitization and observed overshooting of DSA during transplantation.

Case report and results: A 27-year-old female with cutaneous T cell lymphoma was scheduled for HPC transplantation from her HLA-haploidentical half-sister, who carried the HLA-DRB1*13:03:01 allele. The patient had the corresponding DSA. Lacking an alternative donor option at the time, we attempted a desensitization approach by immunosuppression with tacrolimus and mycophenolate mofetil (MMF). Unexpectedly, DSA increased from a mean fluorescence intensity (MFI) of 1835 on day −63 to 9008 on day −7. The MFI increased further during 3 TPE procedures and intravenous immunoglobulin (IVIG) until day −1. After transplantation, the DSA remained elevated despite 2 more TPE/IVIG procedures and graft-versus-host disease prophylaxis with high-dose cyclophosphamide, sirolimus, and MMF. Flow cytometric crossmatch, initially negative, turned positive after transplantation. Primary graft failure occurred and was attributed to antibody-mediated rejection. A second transplantation from a 7/8 HLA-matched unrelated donor, not carrying DRB1*13:03 allele, resulted in successful engraftment.

Conclusion: Unexpected and rapid increases of a DSA can occur despite the use of current desensitization approaches. This is problematic when conditioning has already started, as such increases are unlikely to be overcome by TPE or other interventions for desensitization. Overshoot of DSA in HPC transplantation has rarely been reported. Its cause remains unclear and can include underlying disease, immunotherapy, chemotherapy, or TPE.



S. Hassan et al, Transfusion 2021

Removal of Anti-Thymocyte Globulin by Plasma Exchange

Removal of Anti-Thymocyte Globulin by Plasma Exchange in ABO-Incompatible and Positive Crossmatch Kidney Transplant Recipients

Patricia M. West-Thielke[a,*], Heather J. Ipema[b], Sally Campbell-Lee[c], Enrico Benedetti[a], Bruce Kaplan[a], and James J. Thielke[b]

[a]University of Illinois Medical Center, Division of Transplant Surgery, Chicago, Illinois; [b]University of Illinois at Chicago College of Pharmacy, Department of Pharmacy Practice, Chicago, Illinois; and [c]University of Illinois Medical Center, Department of Pathology, Chicago, Illinois

ABSTRACT

Background. Recipients of ABO-incompatible (ABOI) and positive crossmatch (PXM) kidney transplants are at high risk for antibody-mediated acute rejection. Despite aggressive immunosuppression in high-risk patients, the incidence of acute rejection remains considerably higher than in other groups. No published studies have examined plasma concentrations of anti-thymocyte globulin (ATG) in patients undergoing plasma exchange. The objectives of this study were to compare plasma ATG concentrations before and after plasma exchange in ABOI and PXM kidney transplant patients to determine the amount removed.

Materials and Methods. This prospective pharmacokinetic evaluation enrolled 10 patients undergoing ABOI or PXM kidney transplant at an academic medical center. Blood and waste plasma samples from 5 patients were assayed for total and active ATG concentrations. Patient records were monitored for renal function and rejection rates in the first 6 months post-transplant.

Results. Total ATG concentrations decreased a mean of 59.78 ± 13.91% after each plasma exchange session, and active ATG levels decreased a mean of 56.8 ± 17.08%. Mean daily concentrations reflect a lack of expected ATG accumulation. Only 1 of 4 patients had detectable ATG concentrations after 30 days. After 6 months, the incidence of acute rejection in this sample was 44% and graft survival was 89%.

Conclusions. This is the first study to show that plasma exchange removes a substantial amount of ATG in high-risk kidney transplant patients. Based on these results, we believe these high-risk patients have been traditionally underdosed.

Table 3. ATG Removal by Plasma Exchange*

Patient	POD	% Total ATG Removed	% Active ATG Removed	% Total ATG in Waste Plasma	% Active ATG in Waste Plasma
5	1	68.46	51.67	31.60	88.33
	5	52.10	36.36	46.82	68.18
	9	51.81	55.36	42.06	110.71
6	1	51.67	49.43	64.06	58.05
	5	45.61	48.24	81.03	77.65
	8	52.94	65.86	74.21	61.75
7	1	NA	NA	NA	NA
	5	49.61	41.63	34.12	115.79
	9	86.58	38.87	19.55	99.37
8	1	55.56	54.67	47.85	92.00
	5	74.04	83.21	53.69	17.37
	9	43.51	52.43	43.62	98.06
9	1	81.90	95.55	23.11	9.97
	5	63.39	65.11	23.25	101.70
Mean		59.78	56.80	45.00	67.07
SD		13.91	17.08	19.39	33.25

First study to show that plasma exchange removes a substantial amount of ATG in high-risk kidney transplant patients

P.M. West-Thielke et al, Transplant Proc. 2021

Desensitization in cord blood transplantation

LETTER TO THE EDITOR

A strategy to reduce donor-specific HLA Abs before allogeneic transplantation

Desensitization start 4–6 weeks before transplant:

- Bortezomib 1.3 mg/m2 on days 1, 4, 8 and 11
- Rituximab 375 mg/m2 weekly
- i.v. Ig 1000 mg/kg,
- Plasmapheresis (in which one plasma volume exchanged with a 5% albumin replacement solution, twice weekly)

In most cases: variable combinations of these interventions.

Plasmapheresis continued after stem cell infusion until neutrophil engraftment in three patients with persistently high DSA levels.

Baseline median DSA level 3193 MFI (range: 1045–19 707 MFI) against one or more alleles (average two alleles).

After intervention, the median DSA level: 606 MFI (range: 156–19 333 MFI).

Patients/graft source	*Stem cell source*	*DSA*	*DSA levels before intervention*	*DSA levels after intervention*	*Intervention*	*Engraftment (day)*		*Follow up in months*	*Transplant outcome*
						Neutrophils	*Platelets*		
1 d-UCB	UCB 1	B 40:01 DPB1 01:01	3396 2596	2339 385	PP i.v. Ig Rituximab	NA	NA	6	Initially, UCB 2 engraftment but experienced secondary graft failure
	UCB 2	A 69:01 B 55:01	1104 2704	156 2369					Died due to graft failure and disease relapse
2 d-UCB	UCB 1 UCB 2	DRB1 04:03	1496	None 221	PP i.v. Ig Rituximab	20	34	4	UCB 2 engraftment Died in remission due to CMV disease
3 Haplo/Cord	UCB	A 02:01 DPB1 14:01 DPB1 17:01	4454 8171 7772	2484 19333 1843	PP i.v. Ig Rituximab Bortezomib	14	54	14	UCB engraftment Relapsed 1 year post SCT
	Haplo	None							Alive
4 Haplo/Cord	UCB Haplo	DPB1 02:01 None	2990	300	PP i.v. Ig Rituximab Bortezomib	25	35	10	UCB engraftment Alive in remission
5 Haplo/Cord	UCB Haplo	None DRB1 18:01	2971	2313	i.v. Ig Bortezomib	9	10	8	UCB engraftment Alive in remission
6 Haplo/Cord	UCB Haplo	C 05:01 DPB1 18:01 None	2020 1621	1018 547	i.v. Ig Bortezomib	60	64	7	UCB engraftment Alive in remission
7 Haplo/Cord	UCB	DQB1 03:01 DPB1 03:01	1045 18140	240 423	PP i.v. Ig Rituximab Bortezomib	21	N/A	1	UCB engraftment Died due to sepsis
	Haplo	A 01:01 B 57:01 DRB1 07:01 DQB1 03:01	10 203 4716 19 707 1045	589 2227 2334 240					
8 MUD	MUD	DPB1 02:01	1621	427	PP i.v. Ig Bortezomib	13	11	10	Alive in remission
9 MUD	MUD	DPB1 04:01	1719	623	PP i.v. Ig Bortezomib	16	80	8	Alive in remission
10 MUD	MUD	DPB1 04:02	14369	1601	PP Rituximab Bortezomib	13	14	3	Alive Relapsed

U. Gergis et al, BMT 2014

Platelet transfusions

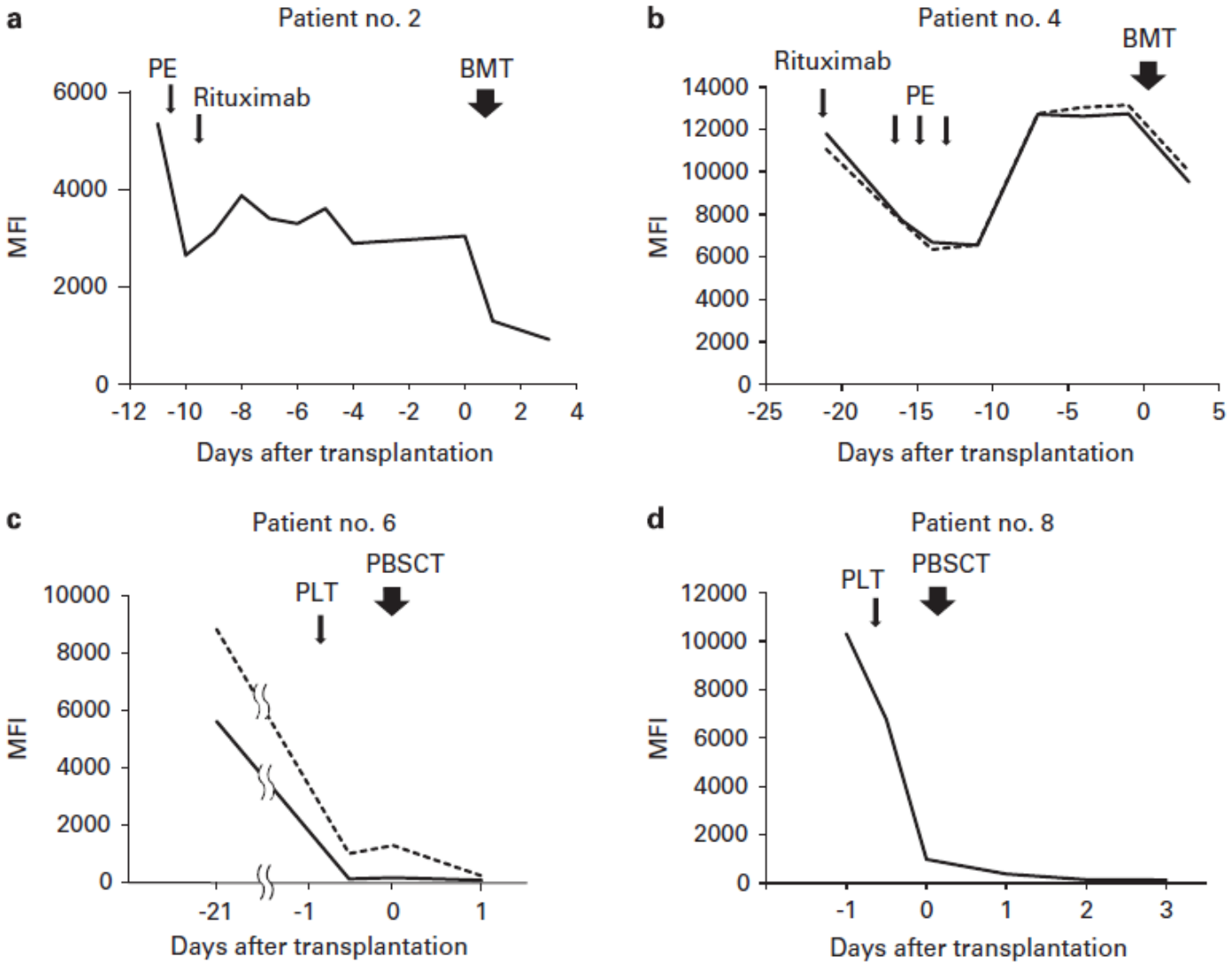
ORIGINAL ARTICLE

Risk and prevention of graft failure in patients with preexisting donor-specific HLA antibodies undergoing unmanipulated haploidentical SCT

11 DSA-positive patients:

- 5 received treatments to decrease DSA levels
- 2 received plasma exchange and rituximab
- 2 received platelet transfusions (40 units) from healthy-related donors having DSA corresponding HLA Ags
- 1 received bortezomib

Platelet transfusion was the most effective treatment option for class I DSA



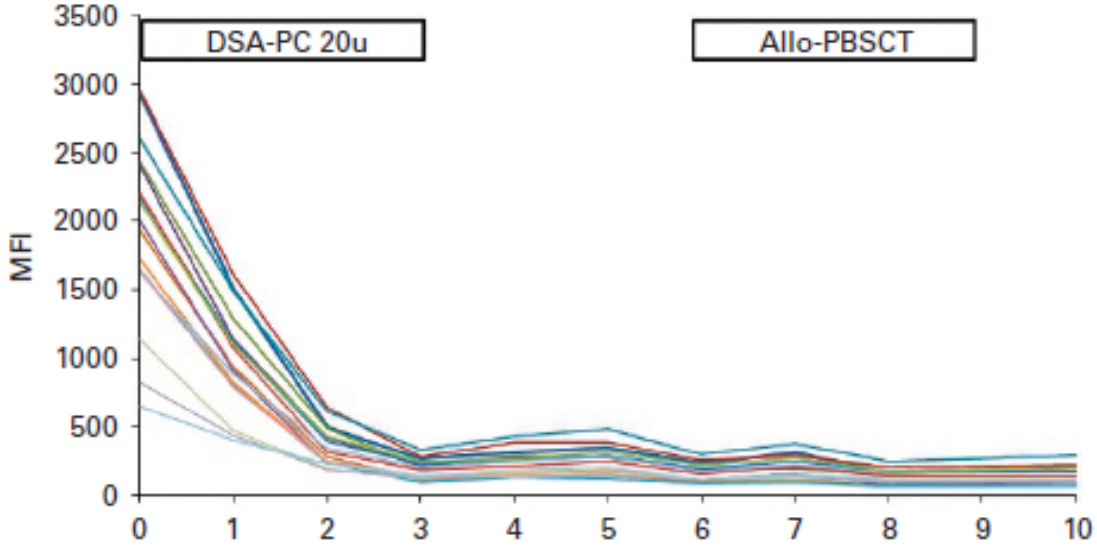
S. Yoshihara et al, BMT 2012

Platelet transfusions

LETTER TO THE EDITOR

Effective desensitization of donor-specific HLA antibodies using platelet transfusion bearing targeted HLA in a case of HLA-mismatched allogeneic stem cell transplantation

T. Yamashita et al, BMT 2017



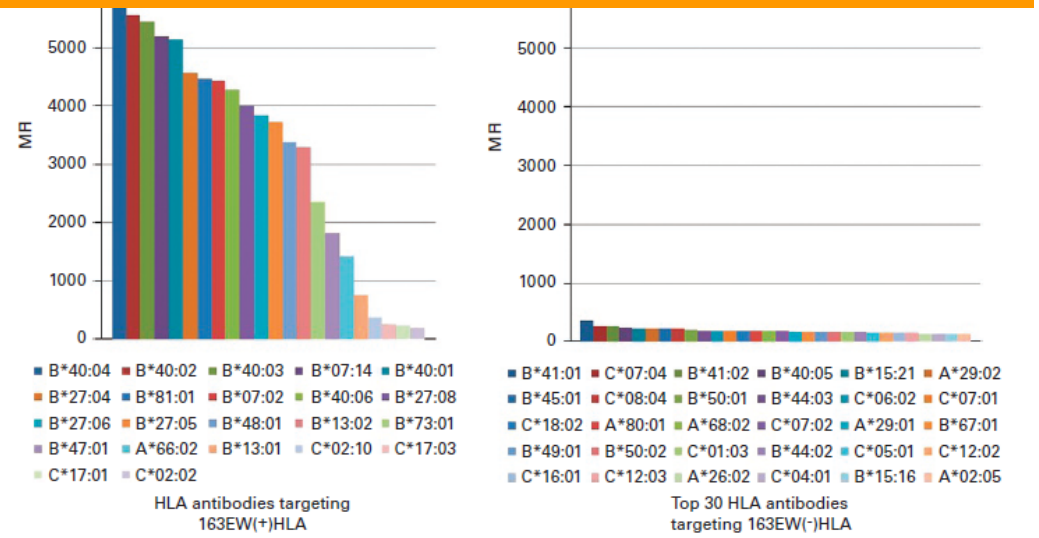
Relapsed patient who developed DSA after the first cord blood transplantation:

Platelets have only class I HLA antigens on their surface

Platelet transfusions can only absorb DSA specific to class I HLA antigens

Chronological monitoring of the titer of HLA antibodies every 1 h during and after the DSA-PC transfusion:
Marked attenuation of not only DSA (anti-HLA B*40:02 Ab) but also other HLA antibodies targeting HLAs containing an epitope, 163EW, which was shared with HLA B*40:02.

Serum MFI level significantly reduced
Engraftment successfully achieved



Plasma exchange and irradiated buffy-coat infusion

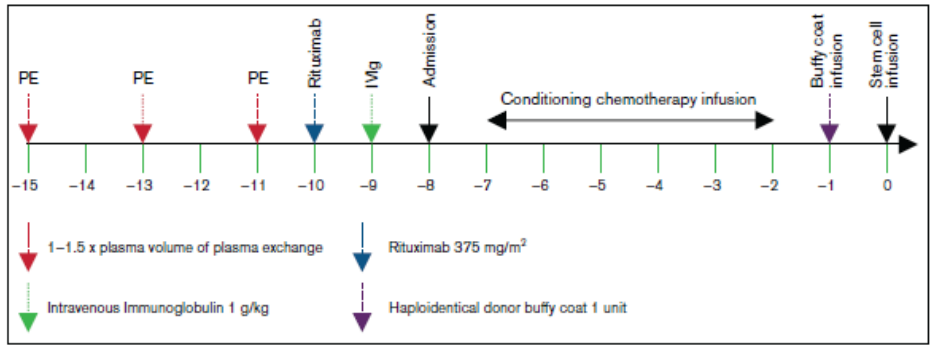
REGULAR ARTICLE

blood advances

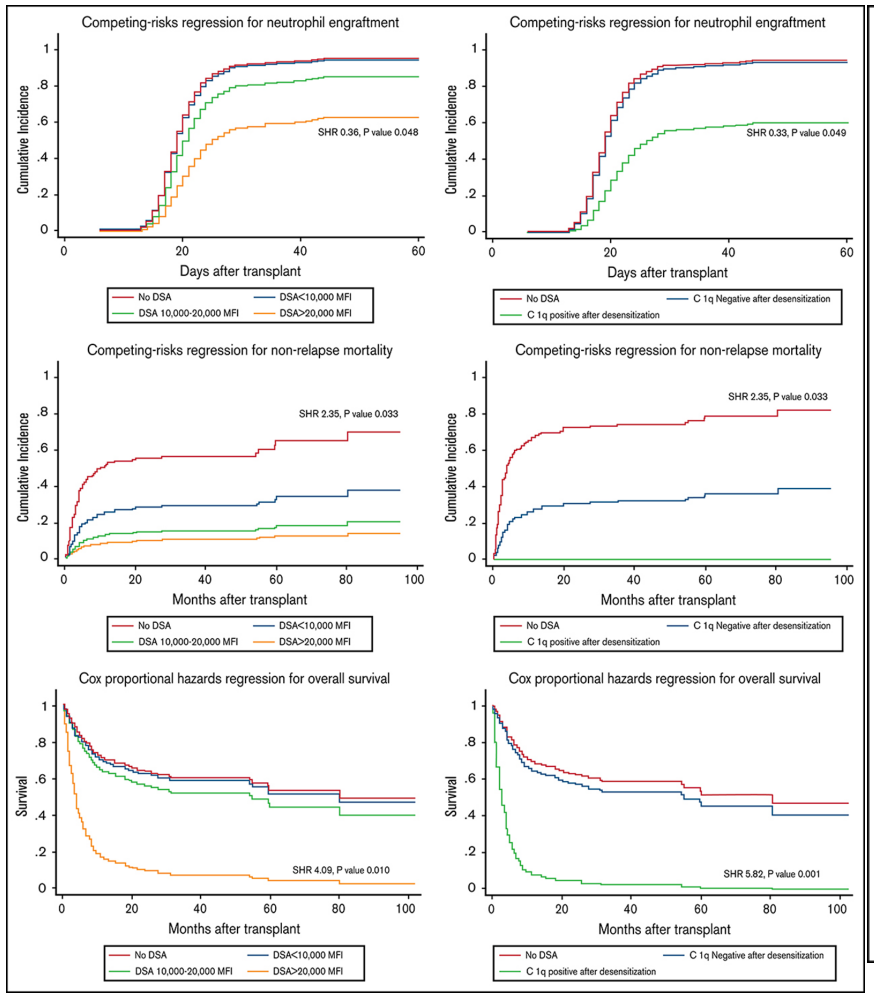
Treatment of allosensitized patients receiving allogeneic transplantation

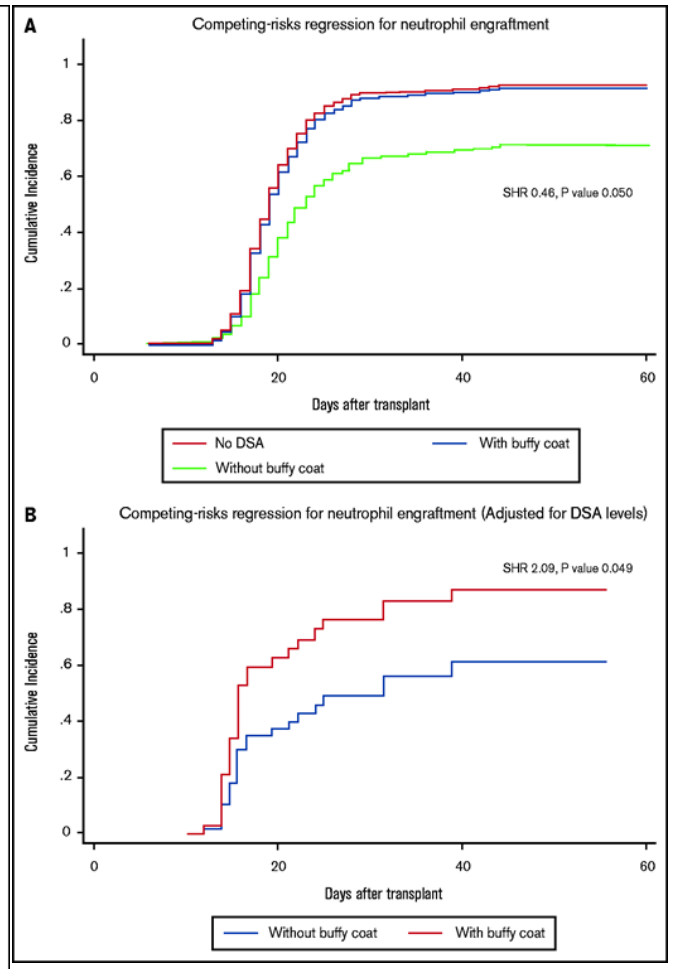
Stefan O. Ciurea,[1,2,*] Monzr M. Al Malki,[3,*] Piyanuch Kongtim,[2] Jun Zou,[4] Fleur M. Aung,[4] Gabriela Rondon,[1] Julianne Chen,[1] Michiko Taniguchi,[5] Salman Otoukesh,[3] Auayporn Nademanee,[3] Stephen J. Forman,[3] Richard Champlin,[1] Ketevan Gendzekhadze,[5,†] and Kai Cao[4,†]

[1]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Hematopoietic Cell Transplantation and Cellular Therapy Program, Division of Hematology-Oncology, The University of California Irvine, Irvine, CA; [3]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, CA; [4]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; and [5]HLA Laboratory, City of Hope, Duarte, CA



Thirty-seven patients (median age 51 years)
Treatment outcomes compared with a control group of Haplo HSCT patients without DSAs (n = 345).
3 sessions of alternate-day plasma exchange (PE) with 1x to 1.5x plasma volume.
Mean DSA level before and after desensitization was 10 198 and 5937 MFI, respectively (mean differences: 4030 MFI).





S.O. Ciurea et al, Blood Adv 2021

14/30 tested patients (46.7%) had C1q positivity, 8/29 tested patients (27.6%) remained positive after desensitization.

Multivariable analysis: patients with initial DSA > 20 000 MFI and persistent positive C1q after desensitization had a significantly lower engraftment rate, higher non-relapse mortality and worse overall survival (OS) than controls.

Outcome of patients with initial DSA < 20 000 MFI and those with negative C1q after treatment were comparable with controls.

Double filtration plasmapheresis

Double filtration plasmapheresis combined with rituximab for donor-specific antibody desensitization in haploidentical haematopoietic stem cell transplantation

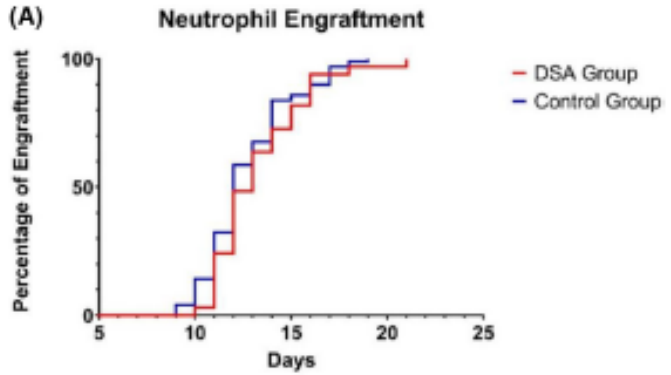
Lizhen Liu[1,2,3,4] | Xinyu Ji[1,2,3,4] | Panpan Zhu[1,2,3,4] | Luxin Yang[1,2,3,4] | Jimin Shi[1,2,3,4] | Yanmin Zhao[1,2,3,4] | Xiaoyu Lai[1,2,3,4] | Jian Yu[1,2,3,4] | Huarui Fu[1,2,3,4] | Yishan Ye[1,2,3,4] | Yibo Wu[1,2,3,4] | Jinping Ying[5] | He Huang[1,2,3,4] | Yi Luo[1,2,3,4]

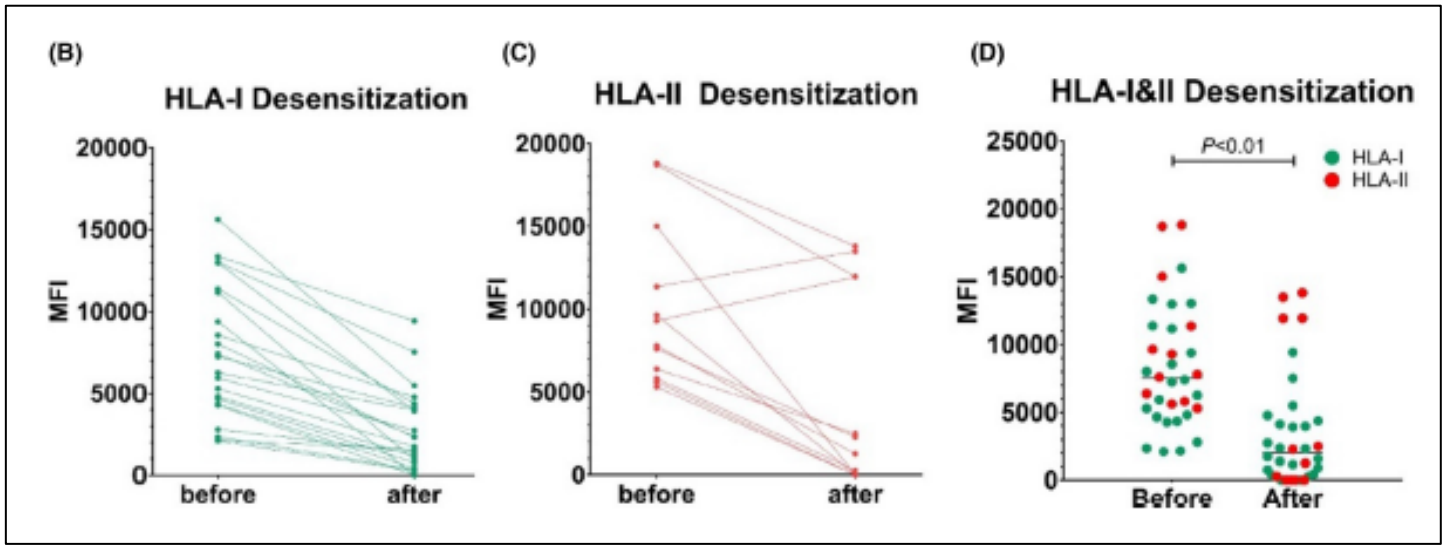
Two sessions of alternate day of DFPP starting 1 week prior to conditioning regimen, followed by a single dose of rituximab (375 mg/m2) the next day after completion of DFPP

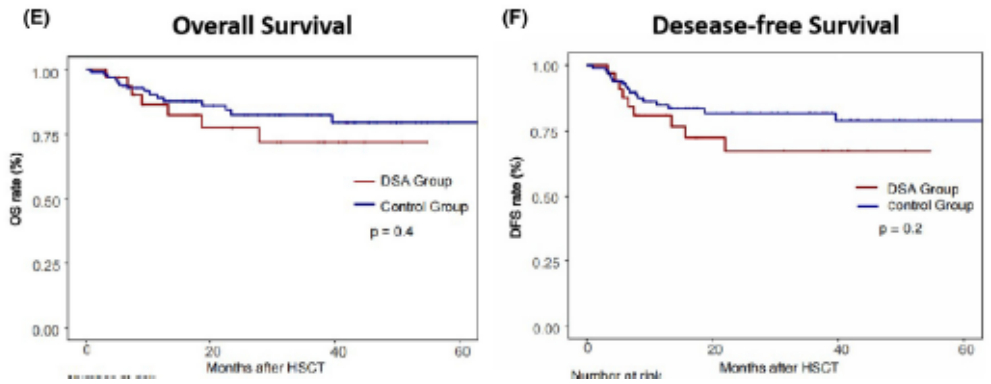
33 patients who had positive DSA, compared with 99 patients with negative DSA (randomly matched as control).

- Median DSA MFI values before DFPP: 7505.88 ± 4424.38
- Median DSA MFI values after DFPP treatment: 2013.29 ± 4067.22 ($p < 0.001$).

All patients in DSA group achieved neutrophil and platelet engraftment







L. Liu et al, Br J Haematol. 2023

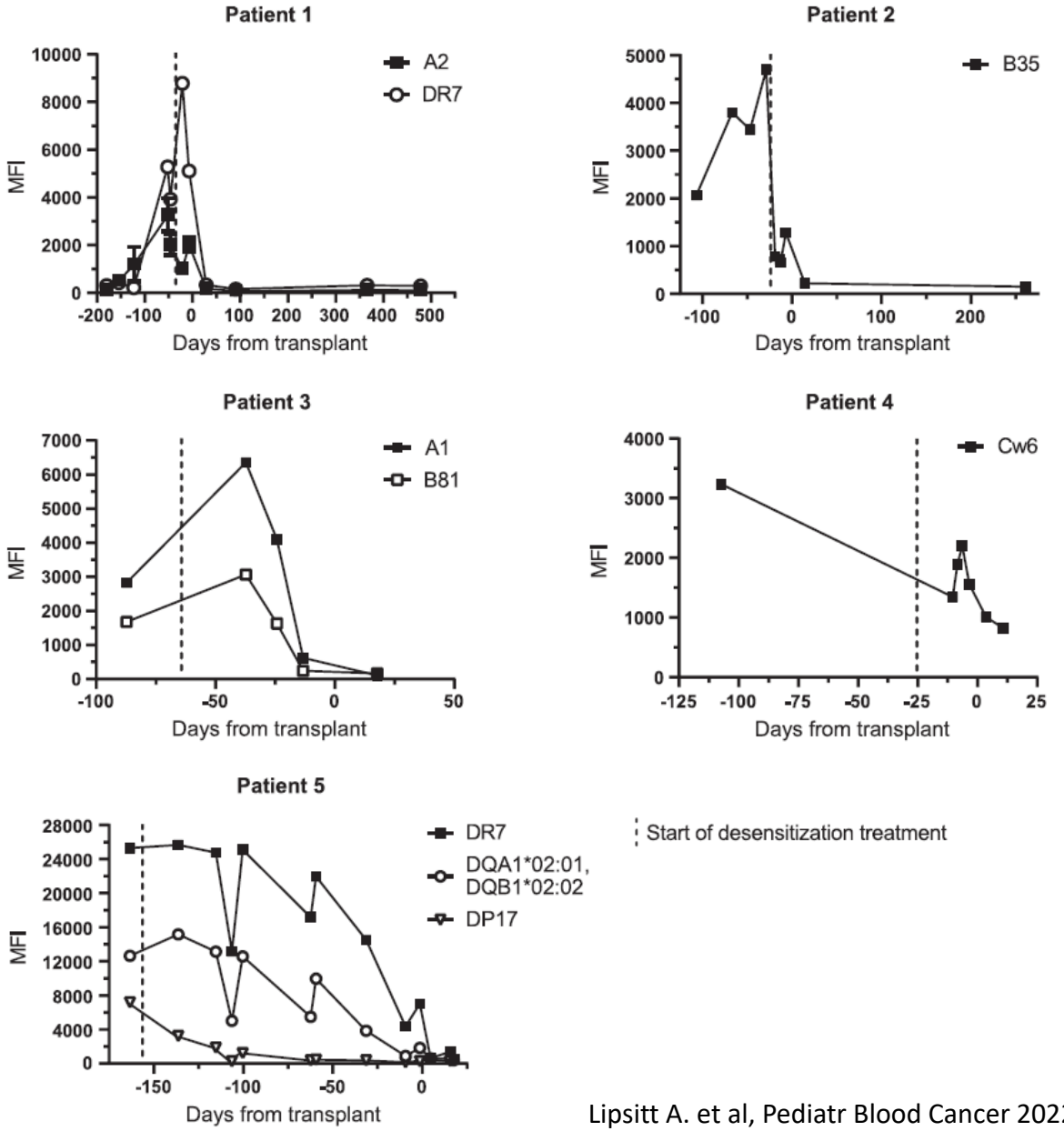
Desensitization in children

Outcomes of patients who underwent treatment for anti-HLA donor-specific antibodies before receiving a haploidentical hematopoietic cell transplant

Amanda Lipsitt[1] | Paula Arnold[2] | Liying Chi[2] | Katharine Carruthers[1] | Sophia Folk[1] | Sallyanne Fossey[3] | Dinesh Keerthi[1] | Ewelina Mamcarz[1] | Ashok Srinivasan[1] | Akshay Sharma[1]

Patient	Sex, age (years), race	Diagnosis	Desensitization treatment
1	Male, 9, Black	SAA	Rituximab (on days −32 and −25 prior to graft infusion), plasma exchange (days −30 through −28 and days −23 through −21), and IVIg (day −18)
2	Female, 9, Hispanic White	AML	Rituximab (days −23 and −16) and plasma exchange (days −21 through −18 and days −14 through −11)
3	Female, 11, Black	SCD	Bortezomib (days −66, −63, −56, −53, −45, −41, −34, and −31), rituximab (days −45, −37, −30, and −24), plasma exchange (days −17, −5, and −13), and IVIg (day −12)
4	Female, 10, Black	SCD	Bortezomib (days −25, −22, −19, and −16), plasma exchange (days −15, −13, and −11), IVIg (day −10), and rituximab (days −9, −1, and +7)
5	Female, 21, Hispanic White	SAA	Initially received a course of bortezomib (days −147, −137, −134, −128, −125, and −117), rituximab (days −147, −140, −143, and −136), and plasmapheresis (days −113, −112, −111, −108, and −107). As the DSA MFI remained elevated, she received a second course consisting of daratumumab (days −79, −71, −64, −57, −50, and −28), rituximab (days −98 and −93), IVIg (days −106, −58, and +4), and plasma exchange (days −21, −17, −15, −13, and −10)

All patients engrafted and alive



Lipsitt A. et al, Pediatr Blood Cancer 2022

The OPBG experience

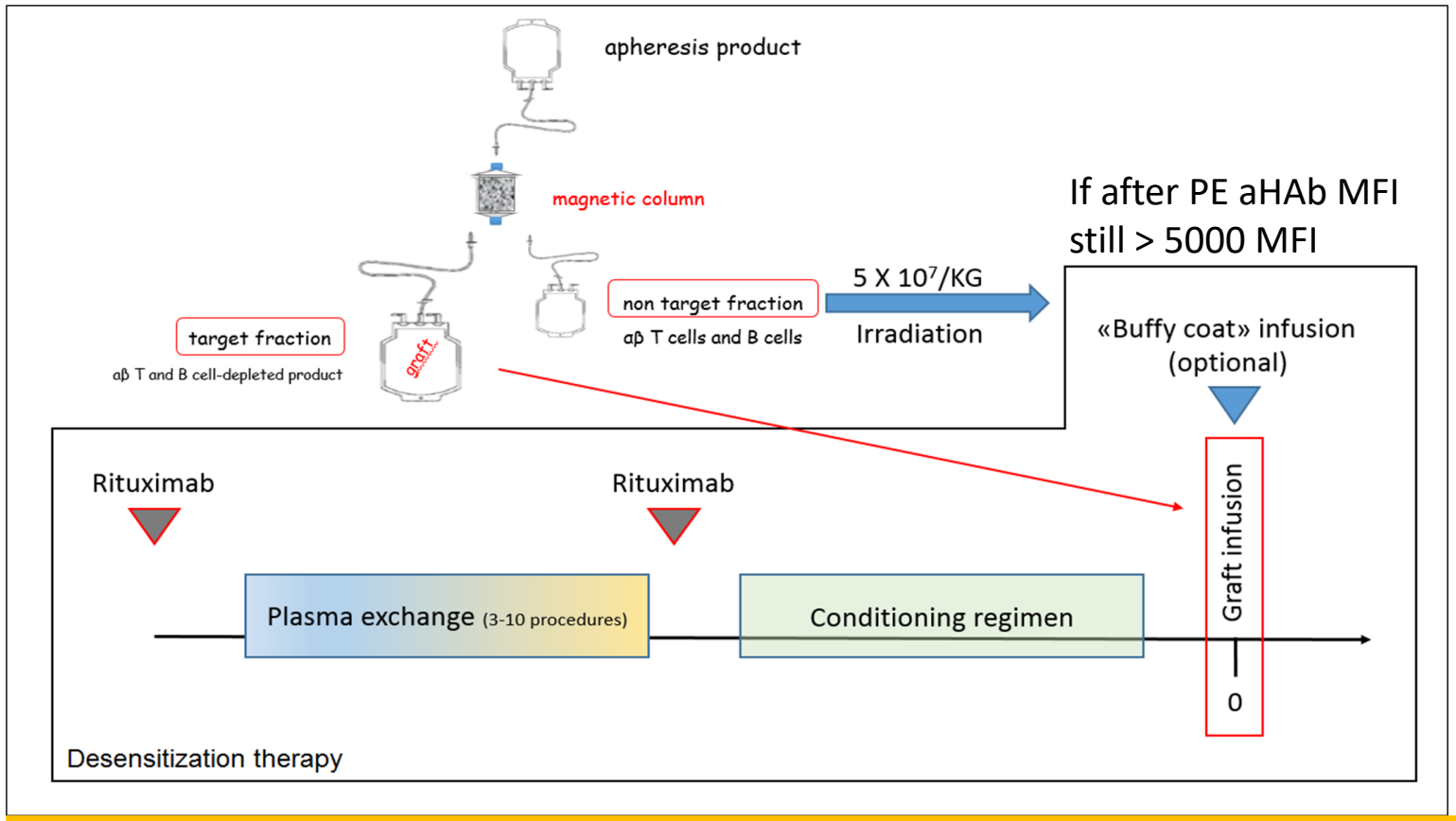


TABLE I	Number	Percentage (%)
Total	14	100
Gender		
Female	8	57
Male	6	43
Age at transplant, years (median and range)	10.7	2.6-16.9
Disease		
Thalassemia Major	8	57
SAA	3	21.5
Fanconi Anemia	2	14.5
PID	1	7
Type of transplant		
T-cell depleted haploidentical	14	100
Source of stem cells		
PBSC	14	100
Conditioning regimen		
Busulfan-Thiotepa-Fludarabine (Thal pts)	9	64
Cyclophosphamide-Fludarabine-200cGy TBI (FA and SAA)	4	29
Treosulfan-Thiotepa-Fludarabine (MDS)	1	7
Sex mismatch		
Yes	5	36
No	9	64

	Pre-desensitization MFI , Median (range)	Post-desensitization MFI, Median (range)	Median reduction (range)	% reduction
Anti-HLA class I	9392 (1420-22418)	2637 (1636-13280)	5280 (range 880-10791	-72%
Anti-HLA class II	2810 (0-13883)	1589 (0-3680)	2414 (range 0-9600)	-56%

Cumulative incidence of GF was 29.2% (95% CI 0.3-49.8) in the 14 treated patients.
No serious advent events associated with the desensitization therapy was recorded

Is there a DSA cutoff more detrimental to engraftment?

- **A positive test for DSA is considered when MFI is above 1,000** (the cutoff of MFI values used varies among transplant centers and laboratories).
- **The significance of low antibody levels remains unclear.** Rejection can occur at any DSA level for MFI>1000, the likelihood of developing PGF increases as the MFI levels increase.
  Low MFI levels (<3000) unlikely represent risk factors for transplantation.
  The incidence of PGF appears to increase with MFI levels above 5000.
- **There is no predictability by IgG mean fluorescence intensity (MFI) as to which of the antibodies will bind C1q because fixation is independent of antibody intensity.**
  Higher MFI levels (>5,000) correlate also with the complement-binding ability (which could contribute to a higher likelihood of rejection.
- **C1q testing is not done yet in many centers**: because of the high association with high DSA levels (>5,000 MFI), it should be presumed that high DSA levels are most likely complement-binding.
- **If C1q testing is positive or the pre-treatment DSA Luminex MFI is >20000, desensitization may not be successful.**

[1] S.O. Ciurea et al, BMT 2018. [2] D.E. Gladstone et al, Hematology Am Soc Hematol Educ Progr. 2017 [3] S. Bramanti et al, BBMT 2020

DSA monitoring and treatment recommendations

Bone Marrow Transplantation
https://doi.org/10.1038/s41409-017-0062-8

REVIEW ARTICLE

Corrected: Correction

The European Society for Blood and Marrow Transplantation (EBMT) Consensus Guidelines for the Detection and Treatment of Donor-specific Anti-HLA Antibodies (DSA) in Haploidentical Hematopoietic Cell Transplantation

Stefan O. Ciurea[1] · Kai Cao[1] · Marcelo Fernandez-Vina[2] · Piyanuch Kongtim[3] · Monzr Al Malki[4] · Ephraim Fuchs[5] · Leo Luznik[5] · Xiao-Jun Huang[6] · Fabio Ciceri[7] · Franco Locatelli[8] · Franco Aversa[9] · Luca Castagna[10] · Andrea Bacigalupo[11] · Massimo Martelli[12] · Didier Blaise[13] · Rupert Handgretinger[14] · Denis-Claude Roy[15] · Paul O'Donnell[16] · Asad Bashey[17] · Hillard M. Lazarus[18] · Karen Ballen[19] · Bipin N. Savani[20] · Mohamad Mohty[21] · Arnon Nagler[22,23]

(1) DSA testing (by Luminex platform and/or cell-based assays) be performed in all candidate patients for haploidentical (or HLA mismatched) donor transplants;

(2) If DSA > 1,000 MFI, C1q testing and/or cell-based assays must be done to further assess the risk to the allograft;

(3) DSA testing should be incorporated in donor selection prior to transplantation; if DSA > 1,000 MFI in the absence of an alternative suitable donor, it is recommended that patients undergo desensitization therapy, especially with high DSA levels (>5,000 MFI) and/or C1q positive, which pose a very high risk to the allograft;

The choice of desensitization protocol may be based on prior local experience. **NO PREFENTIAL STRATEGIES**

NO INDICATION ON PLASMA EXCHANGE STRATEGY, NUMBER OF PROCEDURES, FREQUENCY AND TIMING

S.O. Ciurea et al, BMT 2018

Patients with very high pre-treatment DSA levels (MFI>20.000) or and/or those who remain C1q positive at transplantation have a very high risk of engraftment failure and should not proceed to transplantation or other/additional therapeutic approaches should be investigated.

S.O. Ciurea et al, Blood Adv 2021

The GITMO-AIBT experience

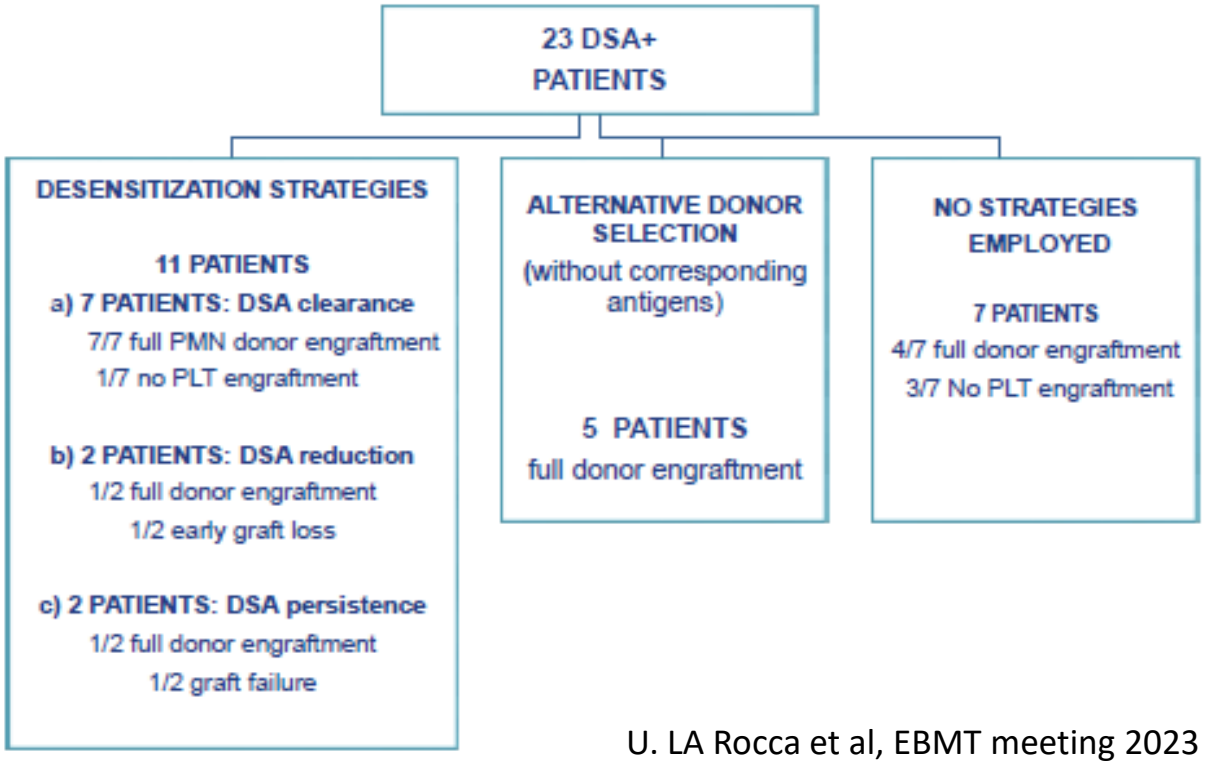
DONOR-SPECIFIC ANTI-HLA ANTIBODIES (DSAS) IN PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM MISMATCHED DONORS, ON BEHALF OF GITMO AND AIBT

Retrospective analysis of 955 patients, transplanted from mismatched donors between 2014 and 2017.

- 804 evaluable (36% females, 64% males)
- Median age: 48 (r: 0-72 years).
- Females: 55% had previous pregnancies, 5% had abortions.
- 88% of patients had previously received blood transfusions.

354 out of 804 patients (44%) were screened for anti-HLA Ab:
Luminex platform employed in 93% of cases

- 91/354 were positive for anti-HLA Ab (25.6%)
- 23 for DSAs
  - 6.5 % of the screened patients;
  - 25.3 % of anti-HLAAb positive patients.



U. LA Rocca et al, EBMT meeting 2023

CONCLUSIONS

- Identification of DSA in the pre-transplant period is associated with an increased risk of GF in recipients of allografts from mismatched/haploidentical donors.
- Importance of a timely and correct DSA screening (especially in case of urgent transplant and absence of alternative unrelated donors).
- Further studies are needed to clarify the impact of DSA with respect of different HLA-loci and the characteristics influecing their specific immunogenicity.
- The availability of a highly-effective and reproducible strategy of desenstitization is crucial where the urgency of the transplant and the immunogenetic characteristics of the donor/recipient pair outweigh the possibility of identifying an alternative donor.
- Prospective studies are needed to harmonize diagnostic measures (methods and cut-off) and therapeutic procedures, as well as to define the best strategy of desensitization.
- Desensitization strategies may also be investigated to further optimize allogeneic HSCT outcome also in case of fully-matched donor (platelet-transfusion refractoriness…).
- Continue cooperation between transplant, transfusion and immunogenetics specialists is warranted.

Dipartimento di Onco-Ematologia e Terapia Cellulare e Genica
IRCCS Ospedale Pediatrico "Bambino Gesù"

Direttore: Prof. Franco Locatelli

GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

Bambino Gesù
OSPEDALE PEDIATRICO

TRAPIANTO EMOPOIETICO E TERAPIE CELLULARI E GENICHE

Marco Becilli
Emilia Boccieri
Roberto Carta
Francesca Del Bufalo
Federica Galaverna
Barbarella Lucarelli
Pietro Merli
Daria Pagliara
Rita Pinto
Francesco Quagliarella
Chiara Rosignoli

MANIPOLAZIONE CELLULARE

Giusy Li Pira
Elia Girolami
Simone Biagini
Lucia Fresolone

IMMUNOGENETICA

Marco Andreani
Paola Giustiniani
Antonio Bianculli

AFERESI TERAPEUTICA

Giovanna Del Principe
Stefania Lazzaro
Giovanna Leone
Antonella Meschini

CENTRO TRIAL ONCOEMATOLOGICO

Maria Pia Cefalo
Andrea Dell'Anna
Caterina Laurieri

Massimo Martino
Fabio Ciceri
Luca Castagna
Stella Santarone
Claudia Del Fante
Mauro Montanari
Elena Oldani
Marco Cioce
Nicoletta Sacchi
Francesca Bonifazi
Stefano Botti
Benedetto Bruno
Michele Malagola
Nicola Mordini
Francesca Patriarca
Simona Piemontese
Alessandra Picardi
Anna Maria Raiola