ACCADEMIA di FORMAZIONE

SIMTI

Attualità nella gestione delle terapie cellulari avanzate

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

Ursula La Rocca

Centro Nazionale Sangue, Istituto Superiore di Sanità

Roma, 25 marzo 2026

La sottoscritta, in qualità di Relatrice
dichiara che

nell'esercizio della Sua funzione e per l'evento in oggetto, NON È in alcun modo portatrice di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le mie funzioni al fine di trarne vantaggio.

TRAPIANTO ALLOGENICO DI CELLULE STAMINALI EMATOPOIETICHE

HLA genotypically identical sibling donors are the gold standard for transplantation purposes, but only 30% patients have such a donor.

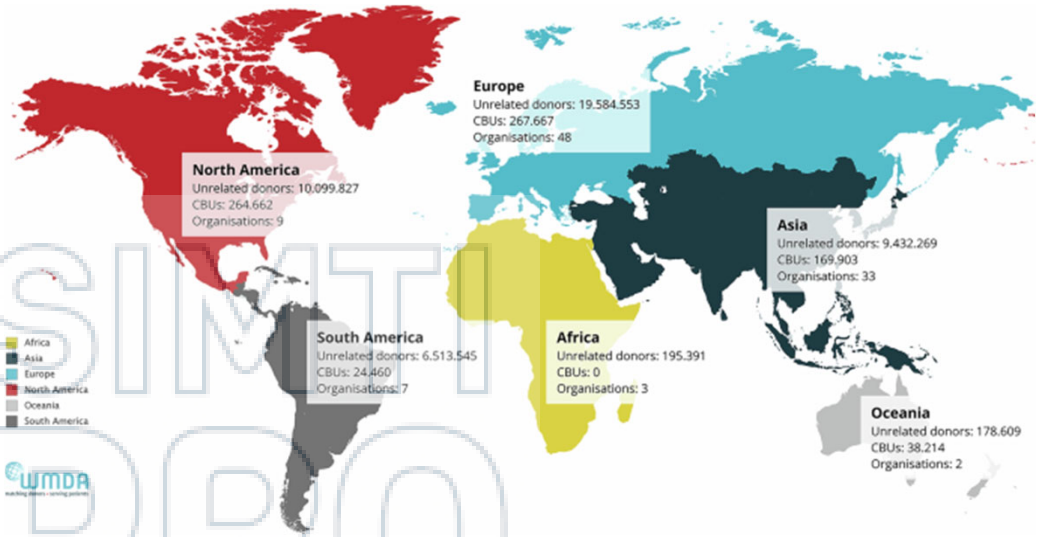
For the remaining ***70% patients' alternative sources of stem cells are a matched unrelated adult volunteer donor, a haploidentical donor or a cord blood unit.***

Ethnic origin (country)[a]	Match 8/8	Match ≥7/8	Match 9/10	Match 10/10	Match 9-10/10	Reference
European (NL)					69%[f]	62
European (UK)					72%	63
European (A)					80%[f]	64
European (D)			20%	61%		17
European (CH)			24%	58%		7
European (NL)			31%	48%		46
European (IT)			32%	43%		65
European (HR)			30%	65%		66
European (USA)	75%	97%				18
African (USA)	18%	71%				18
ME/ NA (USA)[b]	46%	90%				18
Asian (USA)[c]	27-42%	76-88%				18
Hispanic (USA)[d]	34%	80%				18

[a]NL: the Netherlands; UK: United Kingdom; A: Austria; D: Germany; CH: Switzerland; HR: Croatia; USA: United States of America; [b]ME: Middle Eastern, NA: North African; [c]Asian: Chinese, Korean, South Asian, Japanese, Southeast Asian, Vietnamese; [d]Hispanic: South/Central American; [e]9/10 in 13% patients; [f]exceptionally 8/10 matched donors.

Tiercy, Haematologica, 2016

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE



Currently, the proportions of HLA-matched sibling donor transplantation are only 27.7%, 21.0%, and 28.8% of the total allo-SCT population according to activity survey data from Europe, the USA, and China, respectively.

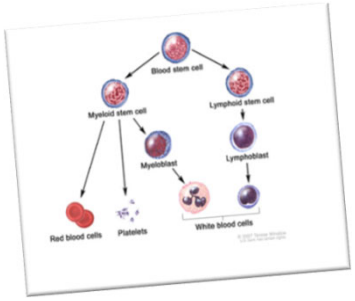
Passweg 2023, Chang 2022, CIBMTR 2022

Historically, matched sibling donors were the preferred allograft source due to their availability and association with lower rates of graft-versus host disease (GVHD) when calcineurin inhibitor (CNI)-based prophylaxis was used.

A.M. Jimenez Jimenez et al. 2025

GRAFT FAILURE

POOR GRAFT FAILURE



GRAFT FAILURE:

- **PRIMARIA: Assenza di iniziale attecchimento dei neutrofili entro il giorno +28.**
- **SECONDARIA: Riduzione della conta assoluta dei neutrofili (ANC) a <0,5 × 10^9/L dopo iniziale attecchimento, associato a perdita del chimerismo.**

POOR GRAFT FUNCTION:

- **Frequente dipendenza da trasfusioni di GR e/o piastrine e/o dal supporto con fattori di crescita, in assenza di altre spiegazioni, quali recidiva di malattia, farmaci o infezioni.**

GRAFT REJECTION:

GRAFT FAILURE causata da distruzione immuno-mediata delle cellule del donatore

Ozdemir ZN, Civriz Bozdağ S. Transfus Apher Sci. 2018
Locatelli F, Lucarelli B, Merli P. Expert Opin Pharmacother. 2014.
EBMT Handbook 2019 A. Sureda, P.A. Bone Marrow Transplant. 2024

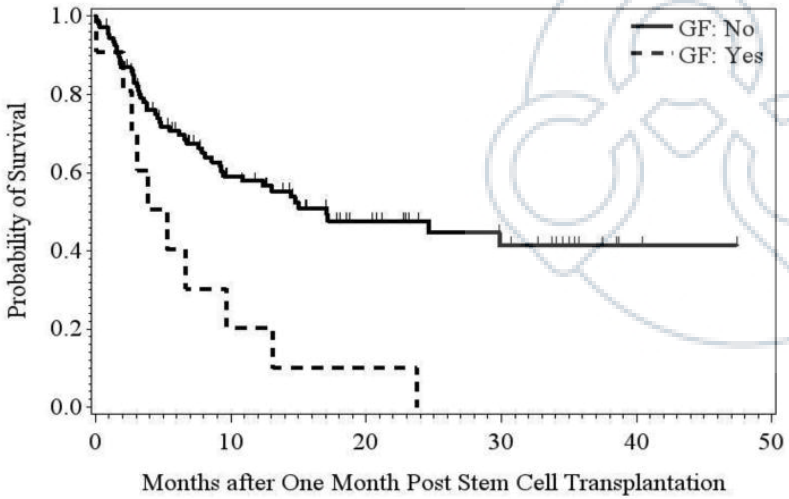
GRAFT FAILURE ED OS

CONDIZIONE GRAVATA

DA PROGNOSI SFAVOREVOLE (infezioni, sanguinamenti)

OS A 5 ANNI < AL 20%

Rondon G, et al. 2008



Ciurea SO, et al. Biol Blood Marrow Transplant. 2015

Published in final edited form as:
Biol Blood Marrow Transplant. 2015 August ; 21(8): 1392–1398. doi:10.1016/j.bbmt.2015.05.001.

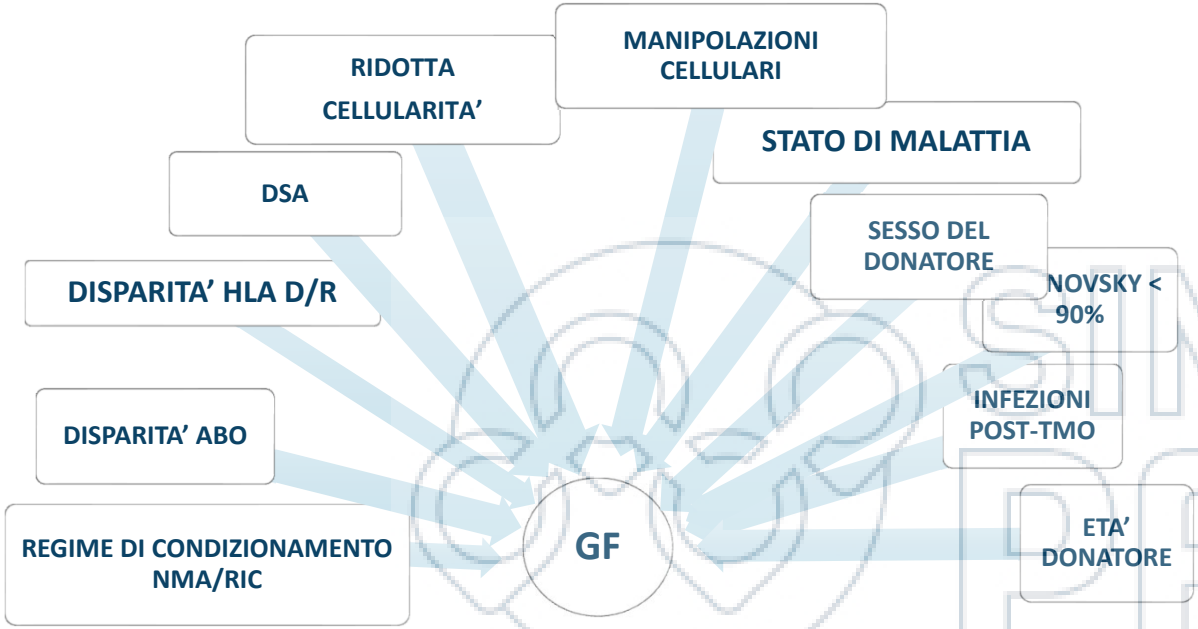
Complement-binding Donor-specific Anti-HLA Antibodies and Risk of Primary Graft Failure in Hematopoietic Stem Cell Transplantation

Stefan O. Ciurea[1], Peter F. Thall[2], Denái R. Milton[2], Titus H. Barnes[3], Piyanuch Kongtim[1], Yudith Carmazzi[3], Asdrúbal A. López[3], Dianne Y. Yap[3], Uday Popat[1], Gabriela Rondon[1], Benjamin Lichtiger[3], Fleur Aung[3], Vahid Afshar-Kharghan[4], Qing Ma[1], Marcelo Fernández-Viña[5], Richard E. Champlin[1], and Kai Cao[3]

Patients with DSA-positive undergoing haploidentical HSCT showed significantly higher rates of primary GF and poorer OS compared with patients with DSA-negative

↓ OS se GF primaria: 5.3 mesi vs. 17.1 mesi

GRAFT FAILURE: CAUSE



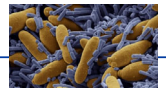
GRAFT FAILURE	
TIPOLOGIA DI TRAPIANTO	INCIDENZA
APLOIDENTICO MANIPOLATO	9%-20%
APLOIDENTICO NON MANIPOLATO	13%
UNITA' CORDONALI	15-20%
MUD	4%
MMUD	10%-15%
SIBLING	< 1%

L'INCIDENZA VARIA TRA IL 4% ED IL 20%
NEI DIVERSI SETTING TRAPIANTOLOGICI CONSIDERATI

ALLOIMMUNIZZAZIONE ANTI-HLA

ANTICORPI → **ANTIGENI/ALLELI HLA ESPRESSI DAL DONATORE**

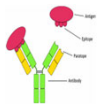
- **GRAVIDANZE** (rischio di allo-sensibilizzazione ↑ con il n. di gravidanze) [1]
  multipare vs maschi: DSA 30% vs 12% (p< 0.0001)[2]
- **PRECEDENTI TRASFUSIONI** (importanza della leucodeplezione) [3-4] /
- **PRECEDENTI TRAPIANTI**
- **ANTICORPI NATURALI** meccanismi di cross-reattività con antigeni batterici, cibi, allergeni[11]
- **ANDAMENTO DINAMICO:** ricomparsa indipendente rispetto alle riesposizioni, e correlato ad infiammazione ed infezioni[11]



IMPORTANZA nell'ambito di:

- TRAPIANTO D'ORGANO SOLIDO (causa di rigetto acuto, iperacuto e cronico)
- M□DICINA TRASFUSIONAL□ (refrattarietà piastrinica; TRALI) [2-3]
- **TCSE graft failure (GF) o poor graft function (PGF)** [4-9]

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE



EPITOPI
CON **PICCOLO NUMERO DI AMINOACIDI (DA 15 A 25)**,
CIASCUNO CON PROPRIA
ANTIGENICITÀ ED IMMUNOGENICITÀ
□PL□TS: □PITOPO FUNZIONAL□

Prevalenza DSA:

1-5% donatori, 24% dei pazienti candidati ad allotrapianto[6-12] - 3-30% aploidentici, 1-10% MUD, 3-7% CBU [13]

[1] Triulzi D, Transfusion 2009. [2] Ciurea SO, Blood 2011. [3] Seftel, MD, Blood 2004 [4] J. Stanworth, BJH, 2015. [5] P. Alvarez, *The Open Respiratory Medicine Journal*, 2015 . [6] Ciurea S O. BBMT 2011. [7] Spelmann S, Blood 2010. [8] Cutler C Blood 2011. [9] Ruggeri A, haematologica 2013. [10] Brunstein CG BBMT 2011. [11] Gladstone D□, BBMT 2013 [12] Morin-Zorman S, Front Immunol 2016, [13] Kongtim et al. 2024

BACKGROUND

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

TEST DI LINFOCITOTOSSICITA' COMPLEMENTO MEDIATA

DSA E RIGETTO ACUTO, IPERACUTO E CRONICO NEI TRAPIANTI D'ORGANO SOLIDO

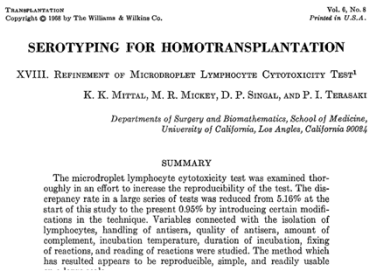
DSA E GRAFT FAILURE NEL TRAPIANTO DI CSE

Effect of HLA compatibility on engrafment of bone marrow transplantation in patients with leukemia or lymphoma
NEJM 1989

1968

1969

1989



TRANSPLANTATION
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Vol. 6, No. 6
Printed in U.S.A.

SEROTYPING FOR HOMOTRANSPLANTATION

XVIII. REFINEMENT OF MICRODROPLET LYMPHOCYTE CYTOTOXICITY TEST[1]

K. K. MITTAL, M. R. MICKEY, D. P. SINGAL, AND P. I. TERASAKI

Departments of Surgery and Biomathematics, School of Medicine, University of California, Los Angles, California 90024

SUMMARY

The microdroplet lymphocyte cytotoxicity test was examined thoroughly in an effort to increase the reproducibility of the test. The discrepancy rate in a large series of tests was reduced from 5.16% at the start of this study to the present 0.95% by introducing certain modifications in the technique. Variables connected with the isolation of lymphocytes, handling of antisera, quality of antisera, amount of complement, incubation temperature, duration of incubation, fixing of reactions, and reading of reactions were studied. The method which has resulted appears to be reproducible, simple, and readily usable

Patel, Terasaki
Significance of the positive cross-match test in kidney transplantation
NEJM 1969

The New England
Journal of Medicine

©Copyright, 1989, by the Massachusetts Medical Society

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 MCSWEEGAN, BRENDA NEISERON, 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.

Abstract We analyzed the relevance of HLA compatibility to sustained marrow engraftment in 269 patients with hematologic neoplasms who underwent bone marrow transplantations. Each patient received marrow from a family member who shared one HLA haplotype with the patient but differed to a variable degree for the HLA-A, B, and D antigens of the haplotype not shared. These 269 patients were compared with 930 patients who received marrow from siblings with identical HLA genotypes. All patients were treated with cyclophosphamide and total-body irradiation followed by the infusion of unmodified donor marrow cells.

The rate of graft failure was 12.3 percent among the recipients of marrow from a donor with only one identical haplotype, as compared with 2.0 percent among recipients of marrow from a sibling with the same HLA genotype (both haplotypes inherited from the same parents) ($P<0.0001$). The incidence of graft failure correlated with the degree of donor HLA incompatibility. Graft failure occurred in 3 of 43 transplants (7 percent) from donors who were phenotypically HLA-matched with their recipient (haplotypes similar, but not inherited from the same parents), in 11 of 121 donors (9 percent) incompatible for one HLA locus, in 18 of 86 (21 percent) incompatible for two loci, and in 1 of 19 (5 percent) incompatible for three loci ($P = 0.028$). In a multivariate binary logistic regression analysis, independent risk factors associated with graft failure were donor incompatibility for HLA-B and D (relative risk = 2.1; 95 percent confidence interval, 1.7 to 2.5; $P = 0.0004$) and a positive crossmatch for anti-donor lymphocytotoxic antibody (relative risk = 2.3; 95 percent confidence interval, 1.8 to 2.8; $P = 0.0038$). Residual host lymphocytes were detected in 11 of 14 patients with graft failure, suggesting that the mechanism for graft failure could be host-mediated immune rejection.

We conclude that donor HLA incompatibility and prior alloimmunization are significant risk factors for graft failure, and that a more effective immunosuppressive regimen than those currently used is needed for consistent achievement of sustained engraftment of marrow transplanted from donors who are not HLA-identical siblings. (N Engl J Med 1989; 320:197-204.)

In multivariate analysis, a positive crossmatch for anti-donor lymphocytotoxic antibody is associated with GF (p=0,0038)
Anasetti et al. 1989

BACKGROUND

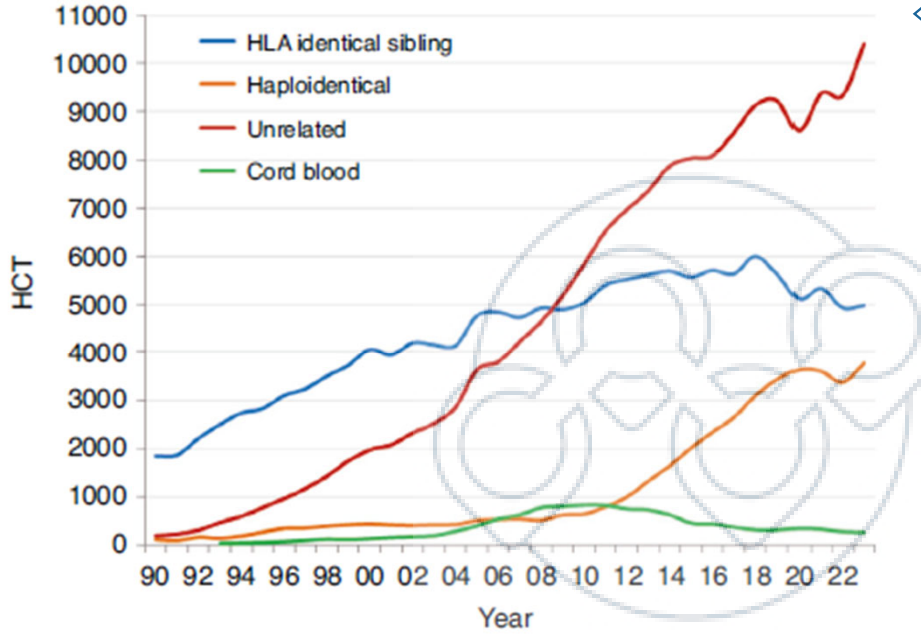


Fig. 4 Change in type of donor for first allogeneic HCT from 1990 to 2023.

Passweg, J.R., *et al. Bone Marrow Transplant* 2025

PROCEDURE TRAPIANTOLOGICHE CON COMPATIBILITA' SEMPRE MINORE

DIAGNOSTICA PIU' SENSIBILE

M□TODI		
Complement dependent microlymphocytotoxicity assay (CDC)	IgG and IgM anti-HLA	Detection of complement fixing antibodies
Solid phase immune-assays (Luminex)	IgG specific anti-HLA	Complement fixing Abs and Non complement –fixing HLA antibodies

Solid-phase assays appear, nowadays,
to be the preferred method for testing and monitoring DSAs,
*with **complement function assessment** and/or the **cell-based FCXM***
***completing the antibodies characterization**.*
Ciurea et al. BMT 2019

EFFECT OF DSA ON ENGRAFTMENT

Transplantation and Cellular Therapy 27 (2021) 687.e1–687.e7

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

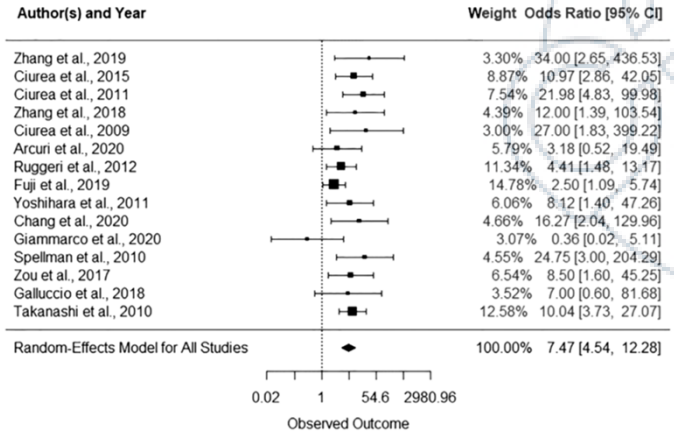
ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article
Analysis

Donor-Specific Antibodies and Primary Graft Failure in Allogeneic Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis

Yiyu Xie[1,2], Jay Parekh[2], Zaixiang Tang[3], Depei Wu[1,*], Xiaojin Wu[1,*]

[1] National Clinical Research Center for Hematologic Diseases, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, China
[2] Yale New Haven Health/Bridgeport Hospital, Bridgeport, Connecticut
[3] Department of Biostatistics, School of Public Health, Medical College of Soochow University, Suzhou, China



A total of 2436 patients were included in these 15 studies.

Patients with DSAs prior to HSCT had a 7.47-fold increased risk of PGF compared with patients without DSA (OR, 7.47; 95% CI, 4.54 to 12.28, P < .001; I2 = 28.91%, P = .1315)

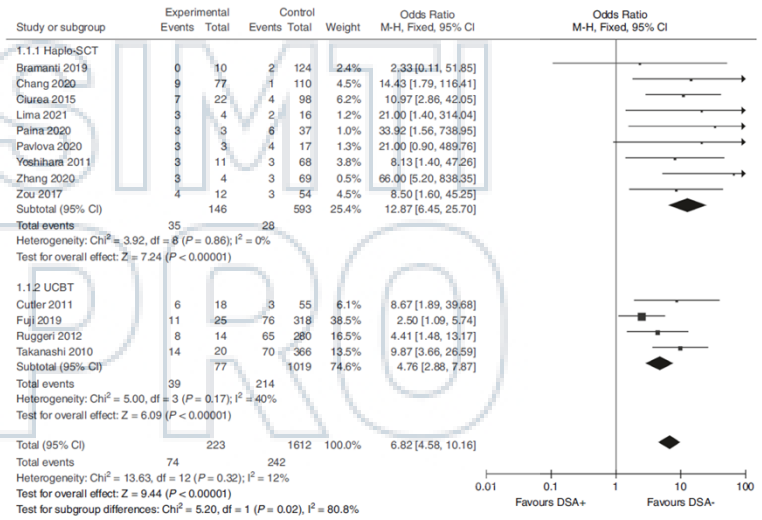
Y. Xie et al. Transplantation and Cellular Therapy 2021

ARTICLE

Check for updates

Effects of donor-specific antibodies on engraftment and long-term survival after allogeneic hematopoietic stem cell transplantation—A systematic review and meta-analysis

Yarui Huang[1,2,4], Chengxin Luo[1,2,4], Guixian Wu[1,2], Xiangtao Huang[1,2], Yaqun Ding[1,2], Zhen Huang[1,2], Jieping Chen[1,2✉], Xi Li[3✉] and Shuangnian Xu[1,2✉]



17 eligible studies were included, involving 2169 patients receiving haplo-SCT or UCBT.

DSAs-positive patients:
- higher risk of GF (OR = 12.87, 95%CI, 6.45–25.70; P < 0.00001; OR = 4.76, 95%CI, 2.88–7.87)
- poorer neutrophil engraftment (HR = 2.20, 95%CI, 1.02–4.73; P = 0.04; HR = 1.83, 95%CI, 1.46–2.30; P < 0.00001)
- worse OS (HR = 3.19, 95%CI, 1.85–5.50; P < 0.0001; HR = 1.68, 95%CI, 1.04–2.71; P = 0.03)
- inferior PFS (HR = 4.25, 95%CI, 1.59–11.40; P = 0.004; HR = 4.83, 95%CI, 1.65–14.12; P = 0.004)

Huang et al. Bone Marrow Transplant. 2023

EFFECT OF DSA ON ENGRAFTMENT

Transplantation and Cellular Therapy 27 (2021) 687.e1–687.e7

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article
Analysis

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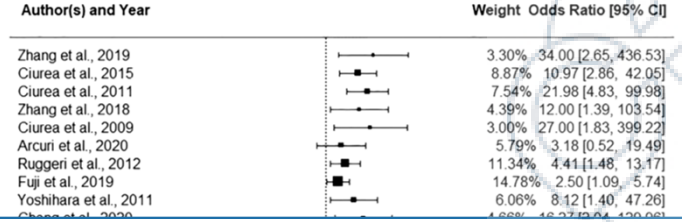
Yiyu Xie[1,2], Jay Parekh[2], Zaixiang Tang[3], Depei Wu[1,*], Xiaojin Wu[1,*]

[1] National Clinical Research Center for Hematologic Diseases, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, China
[2] Yale New Haven Health/Bridgeport Hospital, Bridgeport, Connecticut
[3] Department of Biostatistics, School of Public Health, Medical College of Soochow University, Suzhou, China



ARTICLE

Check for updates

Effects of donor-specific antibodies on engraftment and long-term survival after allogeneic hematopoietic stem cell transplantation—A systematic review and meta-analysis

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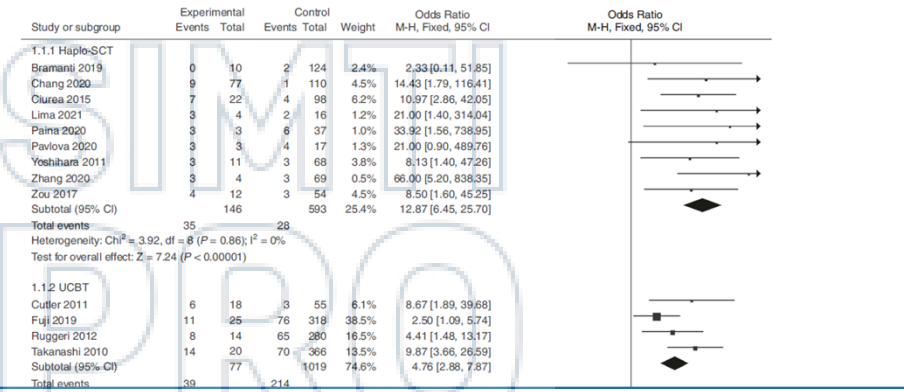


Two systematic reviews and meta-analyses revealed that patients with pre-transplant DSA had 6 to 7-fold higher odds of primary graft failure compared to those without DSA

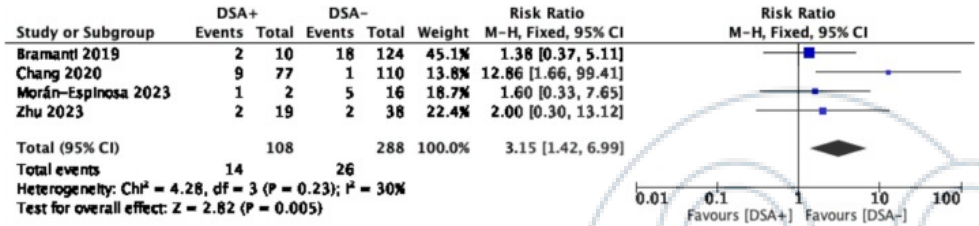
IMPATTO SU OUTCOME

Review

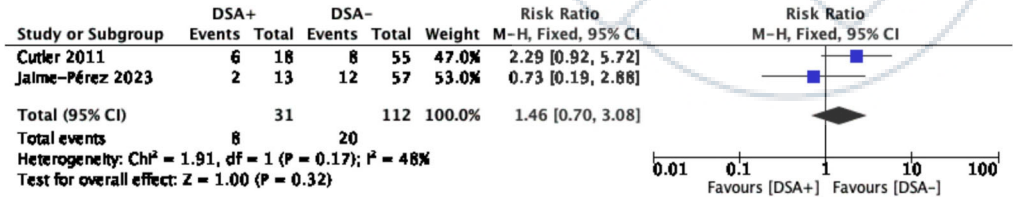
Impacts of donor-specific anti-HLA antibodies on post-transplant clinical outcomes in hematopoietic stem cell transplantation: A systematic review and meta-analysis

Muchen Liu [a], Zhongyu Kang [b], Huan Zhang [c,*]

[a] Hubei University of Medicine, No. 30, Renmin South Road, Maojian District, Shiyan 442000, China
[b] Department of Blood Transfusion, Tianjin First Central Hospital, School of Medicine, Nankai University, Tianjin, Nankai, China
[c] Department of Hematology, Tianjin First Central Hospital, School of Medicine, NanKai University, Tianjin, Nankai, China

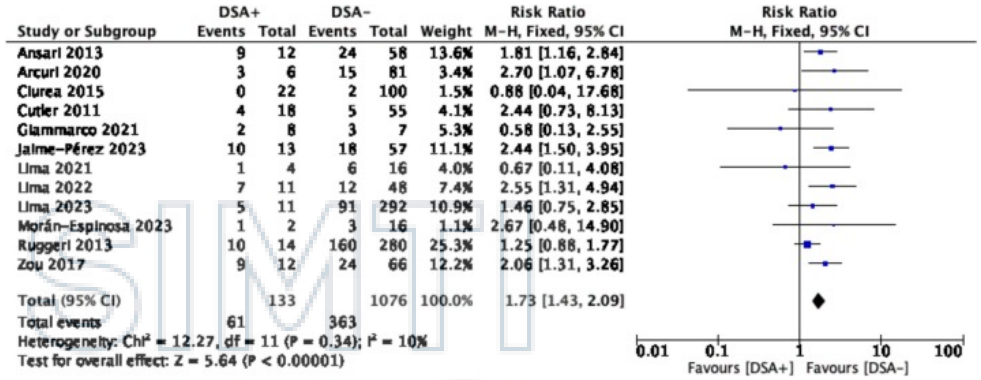


Patients with DSA-positive had a significantly higher risk of PGF compared to patients with DSA-negative (RR 3.15, 95 % CI 1.42–6.99, ***p* < 0.05**).

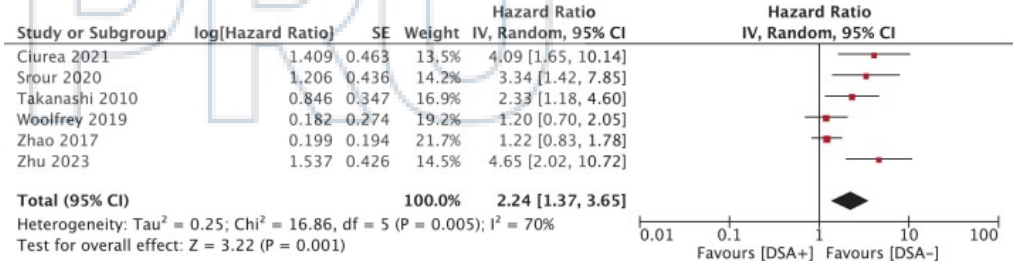


Patients with DSA-positive had a **significantly higher risk of GF compared with patients with DSA-negative (RR 3.92,.95 % CI 2.75–5.59, p < 0.00001).**

- Comprehensive dataset of 32 studies involving 5555 patients, including 557 DSA-positive and 4998 DSA-negative cases, published between 2009 and 2024 from ten countries.
- Broad age range, with median ages spanning from 0 to 74 years.



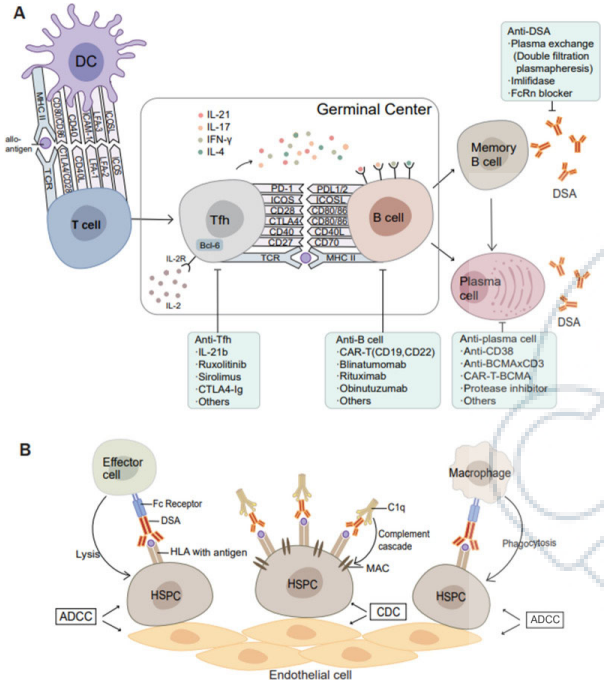
Patients with DSA-positive had **a higher risk of death compared with patients with DSA-negative (RR 1.73, 95 % CI 1.43–2.09, p < 0.00001).**



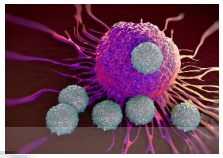
The pooled analysis revealed that patients with DSA-positive had significantly lower OS compared with patients with DSA-negative (HR = 2.24, 95 % CI 1.37–3.65, p = 0.001; Fig. 11).

The findings demonstrate that patients with DSA positive have a significantly **higher risk of PGF, GF, increased mortality, and reduced OS**.
These results underscore the detrimental role of DSAs in HSCT outcomes and highlight the need for effective strategies to mitigate their impacts.

GRAFT REJECTION: PATOGENESI



Zhou et al. 2024



GRAFT REJECTION

CELLULO MEDIATA : REAZIONE DELL'OSPITE CONTRO IL TRAPIANTO MEDIATA DALLE CELLULE T ED NK DELL'OSPITE [1-4]

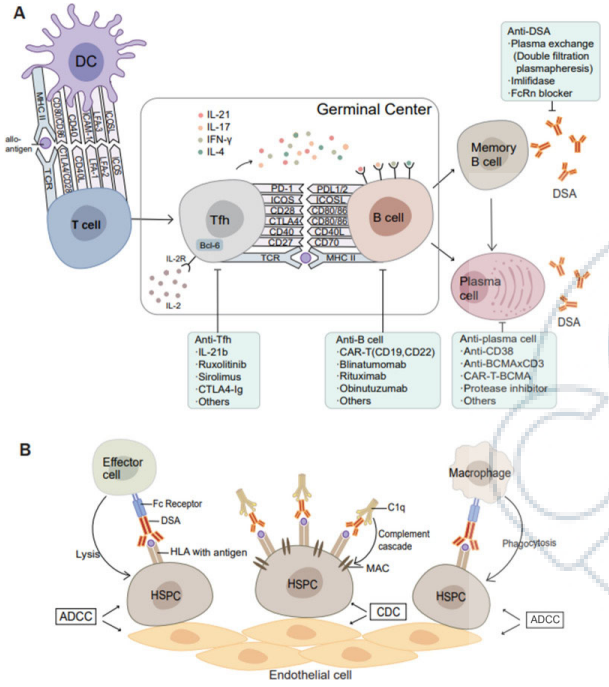
ANTICORPO-MEDIATA: ANTICORPI ANTI-HLA DONATORE SPECIFICI PREFORMATI

CITOTOSSICITA' CELLULO-MEDIATA AB-DIPENDENTE

CITOTOSSICITA' COMPLEMENTO-MEDIATA [5-8]

1 Chang YJ, J Hematol Oncol 2015 2 N.A. Kernan, Transplantation, 1990. 3 K. Doney, Annals of Internal Medicine, 1997 . 4 H. Nakamura Transplantation, 1990. 5 M. Takanashi, Transfusion, 2008. 6 A. Ruggeri, Haematologica, 2013. 7 O. Ciurea, Blood, 2011. 8 S. O. Ciurea, BBMT, 2015 9. A. Loupy,, N. ngl. J. Med. 2013

GRAFT REJECTION: PATOGENESI



Zhou et al. 2024

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

High Risk of Graft Failure in Patients with Anti-HLA Antibodies Undergoing Haploidentical Stem Cell Transplantation

Stefan O. Ciurea[1], Marcos de Lima[1], Pedro Cano[2], Martin Korbling[1], Sergio Giralt[1], Elizabeth J. Shpall[1], Xuemei Wang[3], Peter F. Thall[3], Richard E. Champlin[1], and Marcelo Fernandez-Vina[2]

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[3]Division of Quantitative Sciences, Department of Biostatistics, The University of Texas M. D. Anderson Cancer Center, Houston, TX

Analisi prospettica di 122 TMO aploidentici per ricerca DSA; valutazione retrospettiva test C1q su 22 riceventi. 22/122 pazienti (18%) DSA, 7/22 (32%) GF. Nove DSA+ C1q +, con MFI mediana 15279 (intervallo 1554-28615); 7 C1q negativi, con MFI mediano 2471 665-12254) (p=0,016). 5/9 C1q+ sono rimasti positivi al TMO, con GF; 4 diventati C1q – hanno attecchito (p=0,008). **Ruolo essenziale della capacità di attivare il complemento (C1q positività) e dei livelli di DSA (> 5000 MFI) nella patogenesi del GF.**

ANTICORPI ANTI-HLA DONATORE SPECIFICI PREFORMATI

CITOTOSSICITA' COMPLEMENTO-MEDIATA[5-8]

1 Chang YJ, J Hematol Oncol 2015 2 N.A. Kernan, Transplantation, 1990. 3 K. Doney, Annals of Internal Medicine, 1997 . 4 H. Nakamura Transplantation, 1990. 5 M. Takanashi, Transfusion, 2008. 6 A. Ruggeri, Haematologica, 2013. 7 O. Ciurea, Blood, 2011. 8 S. O. Ciurea, BBMT, 2015 9. A. Loupy,, N. ngl. J. Med. 2013

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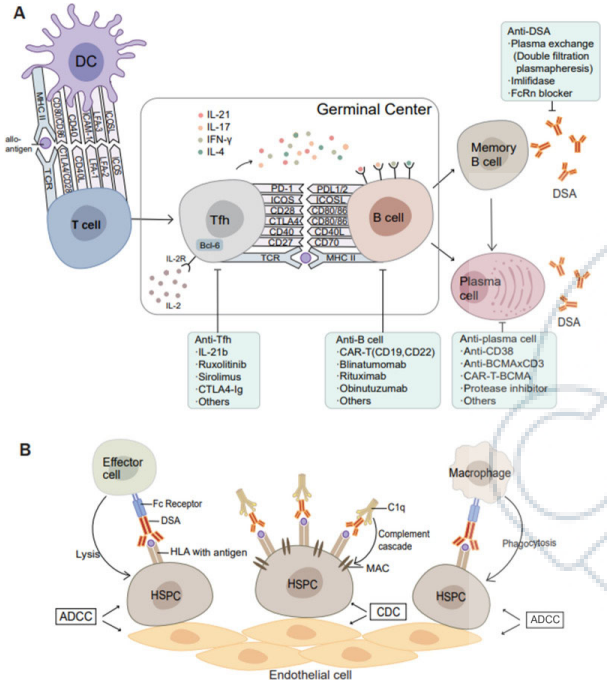

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[2]HLA Laboratory, The University of Texas M. D. Anderson Cancer Center, Houston, TX

Research Article

Donor-Specific Anti-Human Leukocyte Antigen Antibodies Predict Prolonged Isolated Thrombocytopenia and Inferior Outcomes of Haploidentical Hematopoietic Stem Cell Transplantation

Xiaosu Zhao,[1,2] Xiangyu Zhao,[1,2] Mingrui Huo,[1] Qiaozhen Fan,[1] Xuying Pei,[1] Yu Wang,[1,2] Xiaohui Zhang,[1] Lanping Xu,[1] Xiaojun Huang,[1,2,3] Kaiyan Liu,[1] and Yingjun Chang[1,2]

[1]Peking University People's Hospital and Peking University Institute of Hematology, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, No. 11 South Street of Xizhimen, Xicheng District, Beijing 100044, China
[2]Collaborative Innovation Center of Hematology, Peking University, Beijing, China
[3]Peking-Tsinghua Center for Life Sciences, Beijing 100871, China

In vitro experiment performed showed that DSAs could induce apoptosis of CD34+ cells and endothelial progenitor cells (EPCs) in the allografts

1 Chang YJ, J Hematol Oncol 2015 2 N.A. Kernan, Transplantation, 1990. 3 K. Doney, Annals of Internal Medicine, 1997 . 4 H. Nakamura Transplantation, 1990. 5 M. Takanashi, Transfusion, 2008. 6 A. Ruggeri, Haematologica, 2013. 7 O. Ciurea, Blood, 2011. 8 S. O. Ciurea, BBMT, 2015 9. A. Loupy,, N. ngl. J. Med. 2013

DSA E ATTECCHIMENTO

	Donor Study	Nr. Pts	% Anti-HLA Ab+	% DSA+	MFI	Graft Outcome (DSA +/DSA -)
Ciurea et al. 2009	HAPLO Prospective	24	NA	21 (5/24)	>500	GF 75% vs 5% p=0.008
Spellman et al. 2010	MMUD Retrospective	115	37	8.7	>2000	GF 24% vs 1%
Ciurea et al. 2011	MUD - MMUD	592	21	1,4		GF 37.55 vs 2.7% p=0.0014
Yoshihara et al. 2012	HAPLO Prospective	79	20	14	>5000	GF 27% vs 4%
Ciurea et al. 2015	HAPLO Prospective	122	NA	18	>5000	GF 32% vs 4% p < 0,001 DELAYED TIME TO ENFRAFMENT
Chang et a. 2015	HAPLO	345	25.2	11.3		Primary GR 20% vs 0.3% (p=0.002) Primary PGF 27.3 vs 1.9% (p=0.003)
Takanashi et al. 2010	Single UCB	386	23.1	5		Neutrophil Engraftment 32% vs 83% (p=0.0001) DSA+ lower EFS and OS
Cutler et al. 2011	Double UCB	73	NA	24.6		GF 18.2 (DSA vs 1UCB) 57% (DSA vs both UCB) 5.5% (no DSA) p=0.01
Ruggeri et al. 2013	Single UCB Double UCB	294	21	4.7		GF 56% vs 23%

DSA E ATTECCHIMENTO

	Donor Study	Nr. Pts	% Anti-HLA Ab+	% DSA+	MFI	Graft Outcome (DSA +/DSA -)
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Yoshihara et al. 2012	HAPLO	79	20	14	>5000	GF 27% vs 4%

…**considerando il rischio di PGF o GF…**

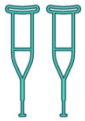
L'ID□NTIFICAZION□ DI DSA pre-TMO rappresenta una CONTROINDICAZION□ a procedere con lo stesso donatore...

□' necessario:

→ **cercare altri donatori**

→ pianificare una **STRATEGIA DI DESENSIBILIZZAZIONE**

STRATEGIE DI DESENSIBILIZZAZIONE

	OPZIONI TRATTAMENTO	TARGET	MECCANISMO D'AZIONE
	• PLASMAFERESI • IMMUNOADSORBIMENTO	ANTICORPI PREFORMATI	RIMOZIONE MECCANICA DEGLI ANTICORPI RESPONSABILI DEL RIGETTO • Plasma- Exchange: Rimozione Completa del plasma • Plasma- Trattamento: Rimozione Selettiva degli anticorpi
	• RITUXIMAB • BORTEZOMIB	• LINFOCITI B CD 20+ • PLASMACELLULE	INIBIZIONE DELLA PRODUZIONE ANTICORPALE AZIONE DEPLETIVA CON CITOTOSSICITÀ COMPLEMENTO MEDIATA E CELLULO MEDIATA, RIDUZIONE DELL'ATTIVAZIONE DEI LINFOCITI T
	• CONCENTRATI PIASTRINICI • BUFFY COAT IRRADIATI DEL DONATORE	ANTICORPI PREFORMATI	NEUTRALIZZAZIONE ANTICORPALE • ADSORBIMENTO DA PARTE DEGLI ANTIGENI DI CLASSE I (C. PIASTRINICI) • ADSORBIMENTO DA PARTE DEGLI ANTIGENI DI CLASSE I E II (BUFFY COAT)
	• IGEV	MULTIPLI	• INTERAZIONE CON I RECETTORI FC SULLE CELLULE FAGOCITARIE E PRESENTANTI L'ANTIGENE • INDUZIONE DELL'APOPTOSI DI LINFOCITI B E PLASMACELLULE • INDUZIONE DELLO SVILUPPO DI LINFOCITI T REGOLATORI. LIMITA REBOUND ANTICORPALE (IGEV)
	INIBITORI DEL COMPLEMENTO • ANTI-C5A: ECULIZUMAB	COMPLEMENTO	INIBIZIONE DELLA CASCATA DEL COMPLEMENTO

STRATEGIE DI DESENSIBILIZZAZIONE

REFERENCE	DONOR TYPE (Nr. of cases)	ANTI-HLA TEST	DESENSITIZATION	DSA POST-DT	OUTCOME
Barge et al. 1989	HAPLO (1)	CDC	PP (2 cycles)	NA	GF
Maruta et al. 1991	MMRD (1)	AHG-CDC	CyA Methylprednisolone 1 week PP DLI	Negative XM	Engraftment
Braun et al. 2000	HAPLO (1)	FCXM	Staphylococcal protein IA	Negative XM	Delayed engraftment
Ottinger et al. 2002	MMRD (2)	DTT-CDC	PP dedicated PLTs transfusion	1 pt -> negative XM 1 patient positive XM	Engraftment GF
Pollack et al. 2004	MMRD (1)	FCXM	PLTs transfusion PP IVIG	Antibodies disappearance at 86 days after HSCT	Engraftment after II HSCT
Norimatsu et al. 2005	MMRD (1)	AHG-LCT	Rituximab (weekly- 4 administrations) dedicated PLTs transfusions (40 units)	Negative AHG-LCT	Engraftment
Ciurea et al. 2009	HAPLO (4)	Luminex MFI > 500	2 weekly doses Rituximab (375 mg/mq) PP (2 cycles)	1 negative 1 low titer 2 high titer	DSA negative and low titer engraftment 2 pt with high titer GF
Yoshihara et al. 2012	HAPLO (5)	Luminex MFI > 500	PP + Rituximab (2) PLTs Transfusions (2) Bortezomib + Dexamethasone (1)	Reduction (2) Reduction (2) Moderate Reduction (1)	All engrafted
Ciurea et al. 2015	HAPLO (12)	Luminex MFI >500	3 PP + Rituximab (1 dose 375 mg/mq) + IVIG 1 g/Kg Kg + donor's buffy coat infusion (5) PP+ Rituximab (1 dose 375 mg/mq) + IVIG 1 g/ (7)	All Pts cleared DSAs after HSCT 5 Pts were C1q positive after treatment	Pts C1q positive after treatment -> GF Pts C1q negative after treatment engrafted
Leffell et al. 2015	HAPLO (13) MMUD (2)	Luminex MFI>1000	PP + IVIG 100 mg/Kg	Mean DSAs Reduction 64.4% 1 pt did not reduce DSAs	All Pts engrafted
Iori et al. 2019	HAPLO (2)	Luminex MFI >1000	Rituximab +PP/PT+IVIG +-PLTs	DSAs Reduction	Both Pts engrafted

TRANSPLANTATION, HEMATOPOIETIC STEM CELL, HLADESENSITIZATION

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice

Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

TRANSPLANTATION, HEMATOPOIETIC STEM CELL, HLA DESENSITIZATION

Incidence: DSA in 3% to 24% of allogeneic hematopoietic stem cell transplantation recipients

Procedure	Category		Grade	
TPE	III		2C	
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	0	7 (96)	11 (16)

DSA = donor-specific antibody directed against human leukocyte antigen (HLA) antigens.

Technical notes

Volume treated: 1 TPV	**Frequency:** Every other day
Replacement fluid: Albumin	

xperience with TP alone for desensitization is limited, with associated concerns of DSA titer rebc suppression.

TABLE 2 Category definitions for therapeutic apheresis

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of
III	Optimum role of apheresis therapy is not established. Decision-making should be individualized.
IV	demonstrates or suggests apheresis to be ineffective or harmful. IRB/Ethics Committee approval is desirable if apheresis treatment is undertaken in these circumstances.

Abbreviation: IRB, Institutional Review Board.

Nelle LG ASFA, l'indicazione alla desensibilizzazione per DSA nel T CSE viene riportata come categoria III, Grado 2C, alla luce del limitato numero di casi riportato in letteratura, in assenza di trial controllati o randomizzati.

Connelly-Smith L, et al. J Clin Apher. 2023

CONSENSUS GUIDELINE EBMT

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]

Received: 23 October 2017 / Revised: 11 November 2017 / Accepted: 17 November 2017

2018

- **Ricerca anticorpi anti-HLA** → entro **1 mese dal trapianto aploidentico/MM**, con metodica Luminex e/o test cell based, parte del work-up di selezione del donatore.
- Se **MFI >1.000**, eseguire **test C1q e/o test cell-based.**
- Tutti i pazienti **con MFI > 1000** devono ricevere un **trattamento desensibilizzante se indisponibili donatori alternativi**, specialmente **con alti livelli di DSA (>5.000 MFI) e/o C1q positivo**, con monitoraggio anticorpale pre- e post-trattamento fino ad ottenimento della clearance anticorpale.
- **Non viene indicato un protocollo definito**: diversi studi hanno riportato diverse **tipologie di schemi**, molti dei quali **aneddotici** e su **piccolo gruppi di pazienti.**

Ciurea et al. BMT 2019

STRATEGIE DI DESENSIBILIZZAZIONE

REFERENCE	DONOR TYPE (Nr. of cases)	ANTI-HLA TEST	DESENSITIZATION	DSA POST-DT	OUTCOME
Zhang R el al. 2020	Haplo (N=5)	MFI > 500	2 U of donor apheresis PLT D-1 + R 375 mg/m2 single dose 1-2 weeks prior to conditioning regimen (if DSA class II positive)	Significant decrease in 5/5	5/5 (100%)
Bailen et al. 2021	Haplo (N=19)	> 1,000	Varied between pts; included R 375 mg/m2, IVIG 0.4 mg/kg/day, MMF 5-10 mg/kg/bid, tacrolimus, PEX, PLT, buffy coat, steroids	Mean reduction 74%	17/19 (89%)
Ciurea S et al. 2021	Haplo (N=37); controls (N=345) - 100% for MFI20,00	> 1,000	PEX 1-1.5 TPV QOD for 3 sessions, starting 1-week prior to conditioning regimen, + R 375 mg/m2 single dose 1 day after PEX completion, + IVIG 1 g/kg 1 dose 1 day after R § donor irradiated buffy coat on	D-1 Mean pre tx DSA - 10,198, Mean DSA post-tx - 5,937 (42% reduction)	100% for MFI < 20,000
Hashem H et al. 2022	Haplo (N=8)	> 3,000	DSA > 8000 MFI: IVIG + R + PEX DSA 3000-8000 MFI: IVIG + R	NA	4/8 (50%)
Shen Y et al. 2023	Haplo (N=13)	> 4,000	IVIG 0.4 g/kg within 72 hours prior to stem cell infusion + R 375 mg/m2 1-2 doses D-16, -9+ HLA-selected PLT infusion 48 hours prior to stem cell infusion DSA reduction	48.3%	13/13 (100%) NE
Altareb M et al. 2023	Haplo (N=5)	> 500	- PEX 1-1.5 TPV for 3 sessions, starting 1-week prior to conditioning regimen, + R 375 mg/m2 single dose 1 day after PEX completion, + IVIG 1 g/kg 1 dose 1 day after R +- donor irradiated buffy	Significant decreased in 3/3	5/5 (100%)

Nel corso degli anni, i diversi gruppi hanno iniziato a porre maggiore attenzione al valore di MFI, riservando trattamenti ridotti a condizioni caratterizzate da MFI più bassi,

LIVELLI DI DSA

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

Biol Blood Marrow Transplant 25 (2019) 1395–1406

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Haploidentical

Donor-Specific Anti-HLA Antibodies in Haploidentical Stem Cell Transplantation with Post-Transplantation Cyclophosphamide: Risk of Graft Failure, Poor Graft Function, and Impact on Outcomes

Stefania Bramanti[1,#], Valeria Calafiore[1,*,#], Elena Longhi[2], Jacopo Mariotti[1], Loretta Crespiatico[2], Barbara Sarina[1], Chiara De Philippis[1], Angela Nocco[2], Armando Santoro[1], Luca Castagna[1]

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Article history:
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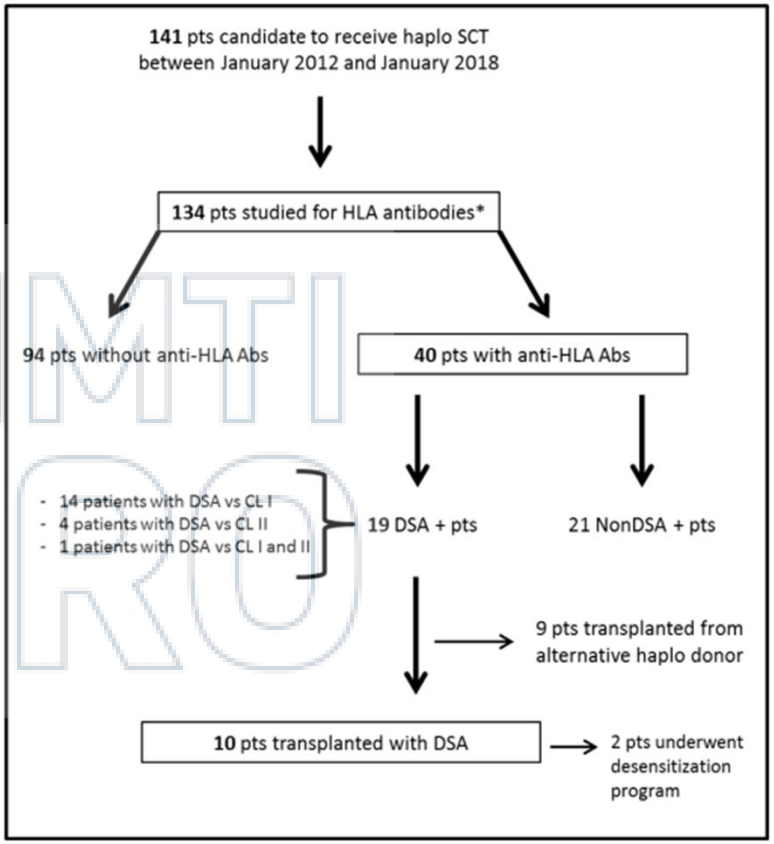
Accepted 18 February 2019

Key Words:
Haploidentical stem cell transplantation
Post-transplantation cyclophosphamide
Donor-specific anti-HLA antibodies
Graft failure
Poor graft function

A B S T R A C T

The presence of donor-specific anti-HLA antibodies (DSA) is associated with a 10-fold increased risk of graft failure in haploidentical stem cell transplantation (haplo-SCT). Consensus guidelines from the European Society for Blood and Marrow Transplantation set a mean fluorescence intensity (MFI) >1000 as a cutoff for DSA positivity. In the absence of an alternative donor, it is recommended that patients undergo desensitization therapy, especially with high DSA levels (>5000 MFI). The aim of this study was to analyze the impact of DSA on risk of graft failure and poor graft function, as well as on major outcomes in a consecutive cohort of patients who were systematically screened for DSA before haplo-SCT. A total of 141 consecutive patients were candidates for unmanipulated haplo-SCT with post-transplantation cyclophosphamide (PT-Cy) at our center between January 2012 and January 2018, and 135 were analyzed for the presence of HLA antibodies. Of these 134 patients underwent haplo-SCT. HLA antibodies were detected in 40 patients, including 19 with DSA and 21 without DSA. Ten of the 19 patients with DSA underwent transplantation using that donor, whereas 2 underwent a desensitization program before transplantation. Only 2 patients experienced primary graft failure (1.4 %), both of whom were without DSA. Twenty patients developed a poor graft function (15%). The 3-year overall survival (OS), 3-year progression-free survival (PFS), and 1-year nonrelapse mortality (NRM) were analyzed according to the presence or absence of DSA. No statistically significant difference was found. No impact of the presence of DSA on the risk of developing graft failure and poor graft function was revealed. Major outcomes of transplantation were analyzed separately in patients with poor graft function and those with good graft function. The 3-year OS, 3-year PFS, and 1-year NRM in good graft function and poor graft function populations were 62% versus 20% ($P < .0001$), 53% versus 20% ($P < .0001$), and 12% versus 40% ($P = .009$), respectively. The presence of low-level DSA in the absence of desensitization did not correlate with the risk of developing graft failure and poor graft function. Patients who experienced poor graft function had worse outcomes than patients with good graft function.



The presence of low-level DSA in the absence of desensitization did not correlate with the risk of developing graft failure and poor graft function.

Bramanti et al. BBMT 2019

LIVELLI DI DSA

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

37 pazienti, età media di 51 anni

DESENSIBILIZZAZIONE: plasmaferesi (P□), rituximab, IG□V, buffy coat irradiato del donatore.

- **Pz con DSA > 20 000 MFI e C1q positivo persistente dopo desensibilizzazione minor probabilità di attecchimento, aumentata mortalità e ridotta OS**
- **DSA iniziale < 20.000 MFI e C1q - dopo trattamento paragonabili ai controlli.**

In conclusion, treatment with **PE, rituximab, IVIg, and donor buffy coat** is effective in promoting engraftment in patients **with DSAs < = 20 000 MFI**

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

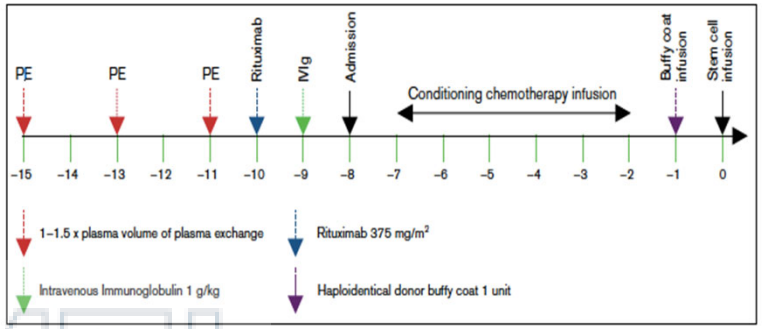
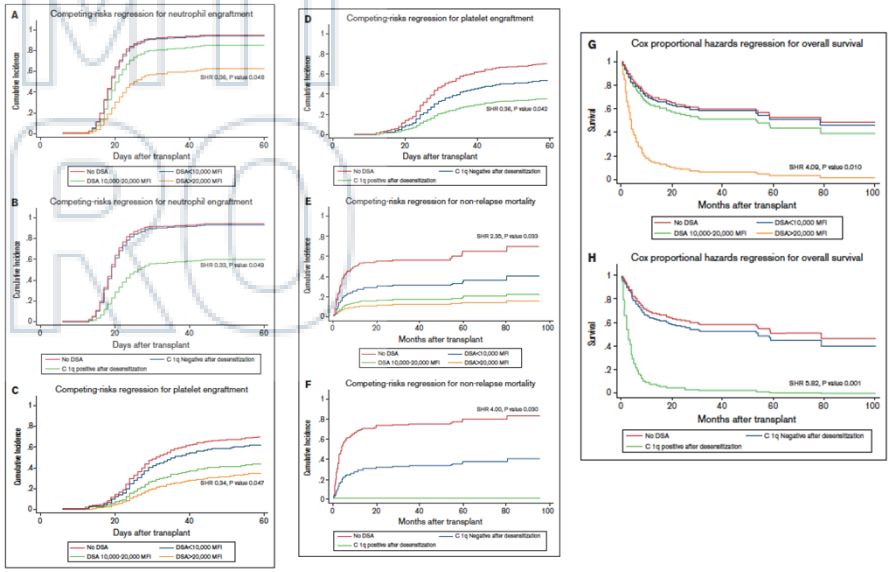


Figure 1. Desensitization protocol.



Ciurea SO, et al. Blood Adv. 2021

DSA E INFEZIONI POST TMO

Research article

Anti-HLA class I donor-specific antibodies are associated with lower overall and event-free survival and late mortality in outpatient haploidentical-related stem cell transplantation from the peripheral blood

José C. Jaime-Pérez *, Casandra Robles-Valverde, Adriana Domínguez-Villanueva, María L. Ruiz-De la Cruz, Nidia K. Moncada-Saucedo, Sandra I. Mendoza-Ibarra, Renata V. Barragán-Longoria, David Gómez-Almaguer

Hematology Department, Internal Medicine Division, Dr. José Eleuterio González University Hospital, School of Medicine, Universidad Autónoma de Nuevo León, Monterrey, Mexico

ARTICLE INFO

Keywords:
HLA
Haploidentical stem cell transplant
Donor-specific antibodies
Graft failure
Reduced-intensity conditioning

ABSTRACT

Background: Donor-specific (DSA) anti-HLA antibodies can adversely influence outcomes of haploidentical hematopoietic stem cell transplantation (haplo-HSCT).
Methods: Patients who received a haplo-HSCT from a sibling after reduced-intensity conditioning (RIC) and had a virtual cross match against donor's HLA typing performed and a positive single-antigen microsphere-based immunoassay test were studied. DSA were considered positive with a mean fluorescence intensity (MFI) ≥ 1000.
Results: Anti-HLA DSA ≥ 1000, median 2623 (range 1000–13,235) MFI were documented in 27/65 (42 %) patients. In 14 (21.5 %) patients, antibodies were anti-HLA class I, in 18 (27.7 %) anti-HLA class II, and in 6 (9.2 %) against both. Overall (OS) and event-free survival (EFS) were lower in patients with anti-HLA Class I DSA (p = 0.026 and p = 0.037, respectively). One-year mortality was higher with anti-HLA DSA of any class (p = 0.009). Nine (64.3 %) of 14 patients with DSA anti-HLA class I died, vs. 11/18 (61 %) with class II DSA (p = 0.238). Anti-HLA DSA were not associated with graft failure (GF) in the cohort. There was no difference in relapse or acute or chronic GVHD in patients with and without DSA.
Conclusion: Anti-HLA Class I DSA > 1000 MFI after haplo-HSCT was associated with lower OS and EFS and higher one-year mortality, but no with GF, acute or chronic GVHD, or relapse.

Table 2
Association of anti-HLA donor-specific antibodies (DSA) of any class with transplant characteristics and outcomes in the whole group of 65 patients.

Variable	Anti-HLA donor specific antibodies		p-value univariate	p-value multivariate
	Present n = 26	Absent n = 39		
Sex mismatch	9 (34.6 %)	16 (41 %)	0.747	
CD34 + /10⁶/kg	10.4 (5.2–39.7)	9.8 (4–18.6)	0.353	
Acute GVHD	10 (38.5 %)	13 (33.3 %)	0.567	
Chronic GVHD	8 (30.8 %)	6 (15.4 %)	0.082	
Infection	15 (57.7 %)	14 (35.9 %)	**0.049**	0.168
Graft failure	4 (15.4 %)	5 (12.8 %)	0.801	
Relapse	7 (26.9 %)	11 (28.2 %)	0.860	
Myeloid recovery (days)	16 (11–24)	15 (11–20)	0.192	
Platelet recovery(days)	18 (11–29)	16 (12–27)	0.583	
PRBC post-HSCT	7 (0–37)	5 (0–20)	0.290	
PRBC transfusion (total)			0.499	
0	3 (11.5 %)	5 (12.8 %)		
1–5	2 (7.7 %)	11 (28.2 %)		
6–10	9 (34.6 %)	6 (15.4 %)		
>10	12 (46.2 %)	17 (43.6 %)		
Post-HSCT platelettransfusion	12 (0–79)	7 (0–37)	0.067	
Platelet transfusion episodes			0.490	
0	0 (0 %)	4 (10.3 %)		
1–5	6 (23.1 %)	10 (25.6 %)		
6–10	5 (19.2 %)	10 (25.6 %)		
>10	15 (57.7 %)	15 (38.5 %)		
Transfusions	25 (96.2 %)	35 (89.7 %)	0.342	
Mortality				
Death, n (%)	16 (61.5 %)	19 (48.7 %)	0.461	
100-day mortality	10 (38.5 %)	7 (17.9 %)	0.092	
1-year mortality	16 (61.5 %)	11 (28.2 %)	**0.015**	**0.019**
Transplant-related mortality	3 (11.5 %)	12 (30.8 %)	0.062	

Abbreviations: PRBC, packed red blood cells; HSCT, hematopoietic stem cell transplant.

- Haplo-HSCT
- **Condizionamento RIC**
- **Nessun protocollo standardizzato di desensibilizzazione**

- **Risultati principali**
- **DSA anti-HLA classe I → ↓ OS, ↓ EFS**
- **DSA (tutte le classi) → ↑ mortalità a 1 anno**
- Nessuna associazione con GF, GVHD o recidiva

Infezioni nel **47.6%** dei pazienti (31/65) , Più frequenti nei pazienti con:

DSA classe I → 71% (p=0.019 univariata; p=0.05 multivariata)
DSA classe II → 50% (non significativa)

Batteri (più frequenti): *E. coli*, *S. pneumoniae*, *Klebsiella*
Virus: CMV
Funghi: *Aspergillus*

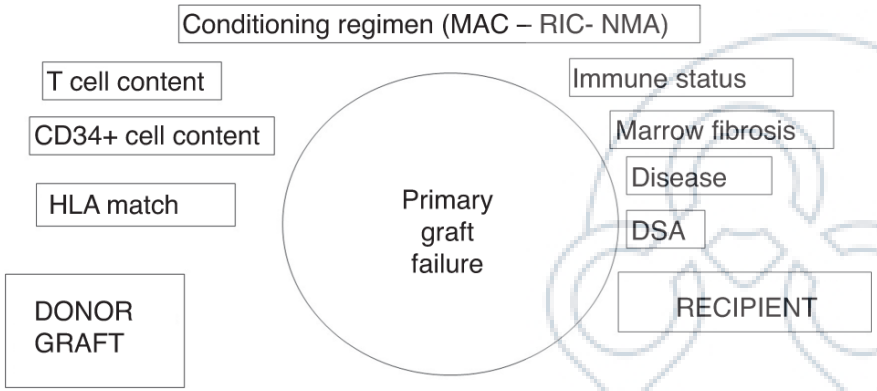
Jaime-Pérez JC, Hum Immunol. 2025

TOWARD A DEFINITION OF IMMUNOLOGICAL RISK FOR PATIENTS WITH ANTI-HLA ANTIBODIES BEFORE STEM CELL TRANSPLANTATION

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

EDITORIAL

Donor specific antibodies (DSA): the only risk factor for primary graft failure?



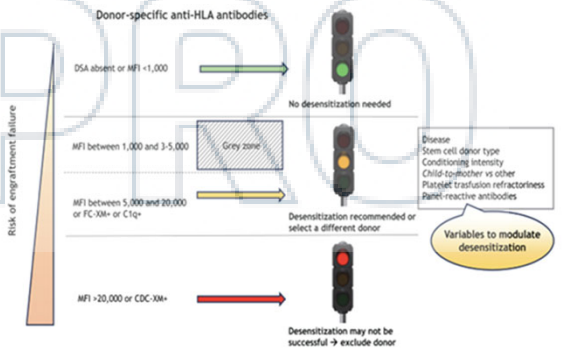
Primary graft failure appears to have a multifactorial pathogenesis, and DSA may play a role in given transplant platforms, but not in others.

Bacigalupo A. Bone Marrow Transplant. 2024

All these elements support the inclusion of disease, conditioning regimen and GvHD prophylaxis, donor type (including stem cell source) and patient-donor relationship within the definition of the immunological risk of a specified patient-donor pair, together with the MFI values and XM or C1q testing results.

That will be expected to account for the risk of engraftment complications and will drive clinicians towards the more appropriate desensitization strategy.

Then, protocols should be modulated according to this risk, aiming at balancing the risk of engraftment complications with that of relapse or infectious complications



Crocchiolo, Blood Transf 2024

Valutare l'alloimmunizzazione nel contesto clinico specifico, per bilanciare in modo ottimale il rischio di mancato attecchimento con quello di infezioni o recidiva, tenendo in considerazione tutte le variabili.

NUOVI APPROCCI

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

Oncol Ther (2024) 12:375–394
https://doi.org/10.1007/s40487-024-00283-6

REVIEW

Desensitization Strategies for Donor-Specific Antibodies in HLA-Mismatched Stem Cell Transplantation Recipients: What We Know and What We Do Not Know

Yang Zhou · Yu-Lun Chen · Xi-Yi Huang · Ying-Jun Chang

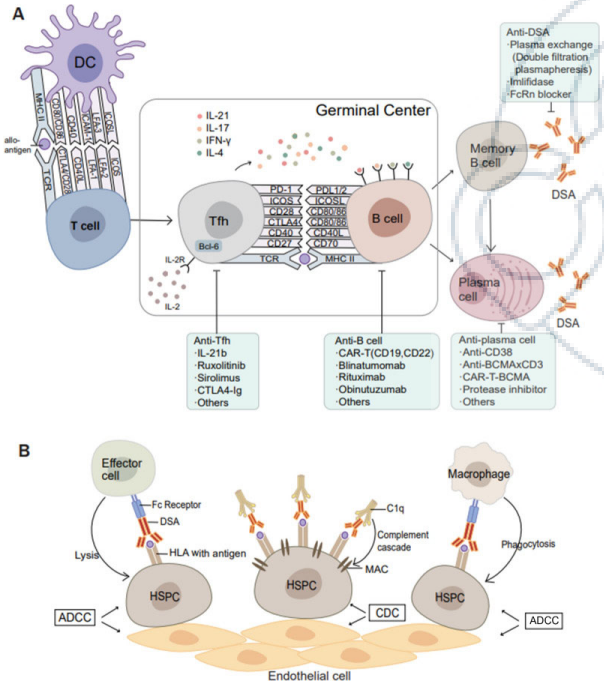


Table 3 Approaches for DSA desensitization in HLA-mismatched allograft settings

Classification of desensitization strategies	Methods currently used and potential approaches in pre-clinical or clinical studies
Removal of circulating levels of DSAs and/or complement-binding DSAs [24, 61, 94]	Plasmapheresis or immunoadsorption, such as double-filtration plasmapheresis
Antibody neutralization/enhancement of DSA clearance [22, 24, 63, 94]	Intravenous immunoglobulin; donor platelets or "buffy coat" (white blood cells) infusion
Therapies targeting B cells [21, 27, 85]	CAR-T cells targeting CD19, rituximab, blinatumomab, mosunetuzumab, and glofitamab
Therapies targeting plasma cells [27, 82–85]	CAR-T cells targeting CD38 and/or BCMA, daratumumab, isatuximab and indatuximab ravtansine*
Therapies targeting Tfh cells [25, 26, 87–91]	Sirolimus, olokizumab, sirukumab, tocilizumab, sarilumab, and abatacept
Complement cascade blockage [23, 63, 94]	Anti-C5a (such as eculizumab)**, intravenous immunoglobulin

DSA donor-specific anti-human leukocyte antigen antibody, *HLA* human leukocyte antigen, *CAR-T* chimeric antigen receptor T cells, *BCMA* B-cell maturation antigen, *Tfh* follicular helper T cells

*Indicates that clinical trials are needed to investigate the efficacy of these methods

**Indicates that anti-C5a has not been used in allogeneic stem cell transplant settings

- **Daratumumab (CR: Li et al. 2022; Ibrahim et al. 2023; Soldarini et al. 2023)**
- **Sirolimus (Studi in vitro ed in vivo; Ma et al. 2024)**
- **Ibrutinib (da esperienze nell'ambito del T cardiaco, Han et al. 2024)**
- **Blinatumumab (potenziali, mai utilizzati come DS)**
- **Tocilizumab (potenziali, mai utilizzati come DS)**
- **CAR-T cells targeting allo-specific memory B cells (Bmems) and long-lived plasma cells (LLPCs) (in vitro)**

Zhou et al. 2024

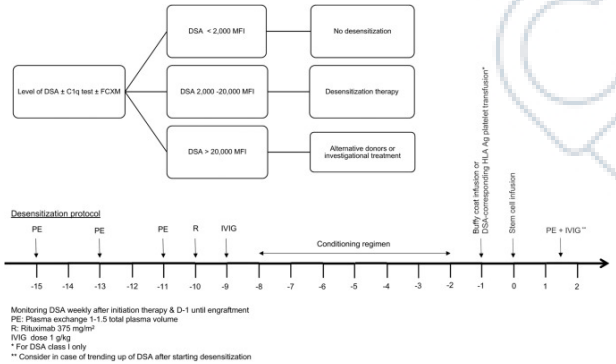
CONSENSUS ASTCT

Transplantation and Cellular Therapy
journal homepage: www.astctjournal.org
ASTCT American Society for Transplantation and Cellular Therapy

Guideline

ASTCT Consensus Recommendations on Testing and Treatment of Patients with Donor-specific Anti-HLA Antibodies

Piyanuch Kongtim[1], Pongthep Vittayawacharin[1], Jun Zou[2], Samer Srour[3], Brian Shaffer[4], Roman M. Shapiro[5], Ankur Varma[6], Joseph McGuirk[7], Bhagirathbhai R. Dholaria[8], Shannon R. McCurdy[9], Amy E. DeZern[10], Nelli Bejanyan[11], Asad Bashey[12], Sabine Furst[13], Luca Castagna[14], Jacopo Mariotti[15], Annalisa Ruggeri[16], Rebeca Bailen[17], Takanori Teshima[18], Huang Xiao-Jun[19], Carmen Bonfim[20], Fleur Aung[21], Kai Cao[21], Paul A. Carpenter[22], Mehdi Hamadani[23], Medhat Askar[24,25], Marcelo Fernandez-Vina[26], Alin Girnita[27], Stefan O. Ciurea[1,*]



Kongtim P, et al. Transplant Cell Ther. 2024

- **To optimize donor cell engraftment, graft function and survival, a donor without corresponding HLA is preferred for a recipient with anti-HLA antibodies, in addition to other donor-related factors affecting transplant outcomes. (Grade of recommendation: B, Levels of evidence 2++)**
- **While the optimal strategy requires further study, DSA desensitization therapy is required to promote hematopoietic engraftment and may lead to improved survival for recipients with DSA, when a suitable alternative donor without the corresponding HLA is unavailable. (Grade of recommendation: C, Levels of evidence 2+)**
- **Higher DSA levels are associated with poor graft function, graft failure, and worse survival. A DSA level >1,000 MFI for CBT and >2,000 MFI for haploidentical and unrelated HSCT might serve as a threshold to initiate desensitization. (Grade of recommendation: C, Levels of evidence 2+)**
- **Multimodality pretransplant desensitization should be used to decrease DSA**
- **For DSA up to 20,000 MFI, plasmapheresis, rituximab, IVIG and infusion of donor-derived HLA antigen (either irradiated buffy coat for the corresponding HLA class I and II or platelet transfusions for corresponding HLA class I only) are recommended.**
- **For DSA >20,000 MFI, patients may require antibody titration (due to bead saturation), and an alternative donor without corresponding HLA should be selected, or else should be treated using an investigational approach.**
- **For DSA 2,000-10,000 MFI in haploidentical HSCT or 1,000- 10,000 MFI in CBT, additional data are needed to determine that patients with these lower DSA levels can be treated with a lower intensity desensitization protocol, such as rituximab with IVIG.**

ARMONIZZAZIONE DIAGNOSTICA

Human Immunology 86 (2025) 111611

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

Research article

A comprehensive comparative assessment of mean fluorescence intensity of luminex single antigen bead tests between laboratories and commercial platforms: A report from the Italian Histocompatibility Network

Antonina Piazza[a], Giovanni Rombolà[b,*], Umberto Maggiore[c], Dario Ciappi[d], Emanuele Cozzi[e], Maria Chiara de Stefano[f], Roberto Crocchiolo[g], Andrea Ricci[f], Massimo Cardillo[h], Valeria Miotti[i], Giuseppe Feltrin[f], Franco Papola[j], on behalf of AIBT Working Group

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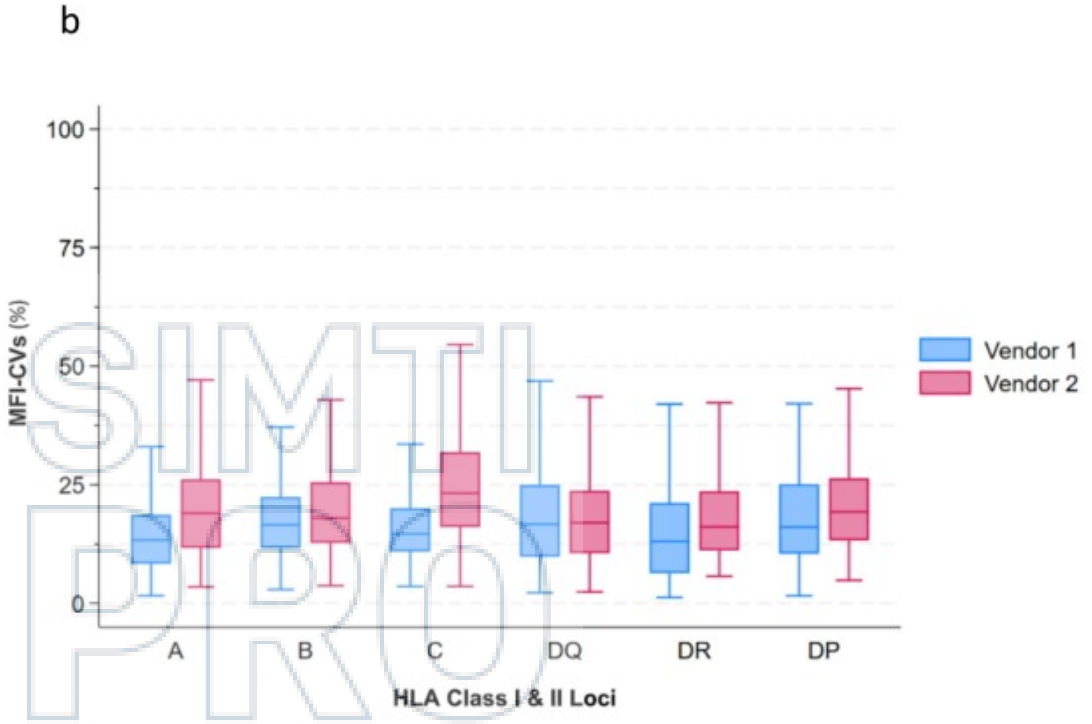


HLA Antigen	CVs (%) Vendor 1	CVs (%)Vendor 2
A	13.3	19.0
B	16.5	18.0
C	14.7	23.2
DQ	16.7	17.0
DR	13.1	16.1
DP	16.1	19.3

Variabilità MFI nei test Luminex tra diversi laboratori e piattaforme commerciali: esiste una **variabilità non trascurabile tra piattaforme commerciali.**

È fondamentale promuovere:

- standard condivisi
- controlli di qualità interlaboratorio
- criteri interpretativi uniformi.

Human Immunology, 2025

DSAs IN HSCT. A STEPWISE PROJECT TO ESTABLISH A BETTER DEFINITION OF THEIR ROLE AND A DESENSITIZATION STRATEGY

2015

GITMO SURVEY

2016

PRELIMINARY EXPERIENCE

2018

PROSPECTIVE UNICENTRIC STUDY

2020

RETROSPECTIVE OBSERVATIONAL STUDY GITMO/AIBT /IBMDR

Bone Marrow Transplantation (2019) 54:1717–1720
https://doi.org/10.1038/s41409-019-0497-1

CORRESPONDENCE

Anti-HLA donor-specific antibodies in allogeneic stem cell transplantation: management and desensitization protocol

Ursula La Rocca[1] · Maria Paola Perrone[2] · Alfonso Piciocchi[3] · Paola Cinti[2] · Walter Barberi[1] · Maria Gozzer[2] · Mahnaz Shafii Baftil[2] · Giovanni Fernando Torelli[1] · Luisa Quattrocchi[1] · Paola Gesuiti[2] · Roberto Lattanzi[2] · Claudio Cavallari[2] · Roberto Ricci[1] · Luca Laurenti[2] · Robin Foà[1] · Gabriella Girelli[2] · Anna Paola Iori[1]

Received: 4 September 2018 / Revised: 5 December 2018 / Accepted: 2 February 2019 / Published online: 4 March 2019

Donor specific anti-HLA antibodies in hematopoietic stem cell transplantation. Single Center prospective evaluation and desensitization strategies employed

Ursula La Rocca[1], Maria P. Perrone[2], Alfonso Piciocchi[3], Walter Barberi[3], Paola Gesuiti[3], Luca Laurenti[3], Paola Cinti[3], Maria Gozzer[3], Manhaz Shafii Bafti[3], Daniela Carmini[3], Nadia Cinelli[3], Claudio Cavallari[3], Gianluca Giovannetti[3], Roberto Ricci[3], Gabriella Girelli[3], Robin Foà[3], Maurizio Martelli[3], Serelina Coluzzi[3], Anna P. Iori[3]

Donor-specific anti-HLA antibodies (DSAs) in patients undergoing allogeneic hematopoietic stem cell transplantation from mismatched donors on behalf of GITMO and AIBT

Ursula La Rocca[1,*], Roberto Ricci[1], Alfonso Piciocchi[2], Walter Barberi[1], Elena Oldani[1], Alida Dominietto[1], Raffaella Cerretti[1], Alessandra Picardi[1,37], Francesca Bonifazi[2], Riccardo Saccardi[1], Maura Faraci[3], Giovanni Grillo[38], Lucia Farina[39], Benedetto Bruno[39], Anna Grassi[1], Anna Proia[39], Elena Tagliaferri[14], Giuseppina De Simone[39], Michele Malagola[16], Michela Cerno[37], Simone Cesaro[38], Paolo Bernasconi[39], Lucia Prezioso[40], Paola Carluccio[39], Nicola Mordini[33], Matteo Pelosini[33], Attilio Olivieri[34], Patrizia Chiusolo[35], Stella Santarone[16], Michele Cimminiello[37], Roberto Crocchiolo[39], Franco Papola[38], Gianni Rombolà[39], Nicoletta Sacchi[39], Valeria Miotti[39,41], Lia Mele[39,41], Benedetta Mazzi[39,41], Fabio Ciceri[39], Massimo Martino[16], Anna Paola Iori[1]

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

STUDIO RETROSPETTIVO (Policlinico Umberto1)

Bone Marrow Transplantation
https://doi.org/10.1038/s41409-019-0497-1

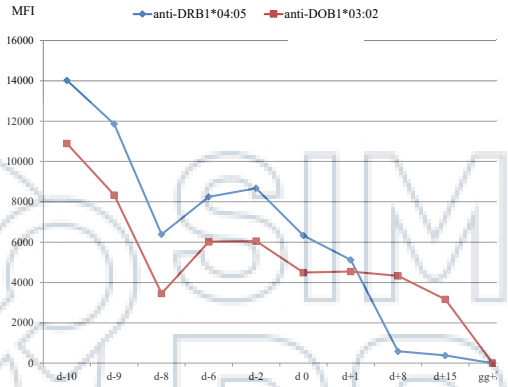
CORRESPONDENCE

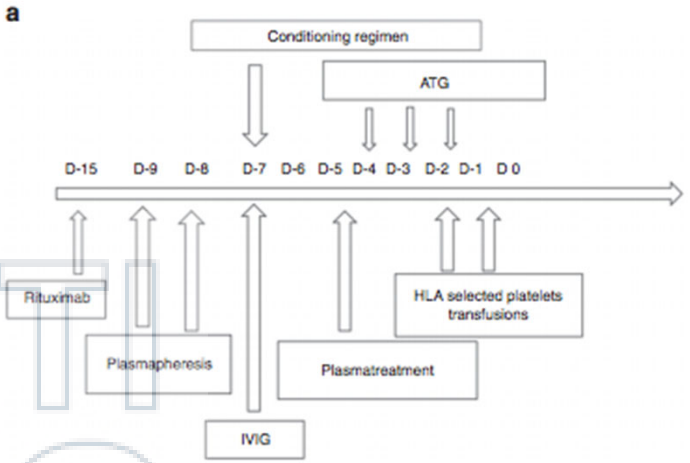
Anti-HLA donor-specific antibodies in allogeneic stem cell transplantation: management and desensitization protocol

Ursula La Rocca[1] · Maria Paola Perrone[2] · Alfonso Piciocchi[3] · Paola Cinti[2] · Walter Barberi[1] · Maria Gozzer[2] · Mahnaz Shafii Baftii[2] · Giovanni Fernando Torelli[1] · Luisa Quattrocchi[1] · Paola Gesuiti[2] · Roberto Lattanzi[2] · Claudio Cavallari[2] · Roberto Ricci[1] · Luca Laurenti[2] · Robin Foà[1] · Gabriella Girelli[2] · Anna Paola Iori[1]

Received: 4 September 2018 / Revised: 5 December 2018 / Accepted: 2 February 2019

65 pazienti candidati a TCS
Anti-HLA Ab: **20 pz (30%)**
DSA: **4 pz (6.15%)** → 2/4 pz: selezione D alternativo
2/4 pz: DESENSIBILIZZAZIONE



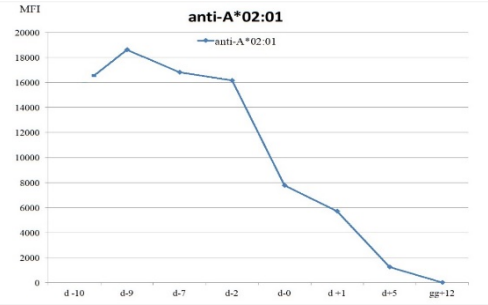


IMMUNIZZAZIONE ANTI-HLA IN BASE A SESSO ED EVENTI IMMUNIZZANTI

FEMMINE	
	p
GRAVIDANZE/ABORTI (%)	1.000
TRASFUSIONI (%)	0.895
MASCHI	
TRASFUSIONI (%)	0.918

IMMUNIZZAZIONE ANTI-HLA IN BASE ALLE TRASFUSIONI

		NO	SI	p
TOTALE (%)		6 (9.2)	59 (90.8)	1.000
Anti-HLA Ab (%)	NEG	4 (66.7)	41 (69.5)	
	POS	2 (33.3)	18 (30.5)	



La Rocca et al. BMT 2019

STUDIO PROSPETTICO (Policlinico Umberto1)

HEMATOPOIETIC STEM CELL TRANSPLANTATION AND CORD BLOOD BANKING

Original article

Donor specific anti-HLA antibodies in hematopoietic stem cell transplantation. Single Center prospective evaluation and desensitization strategies employed

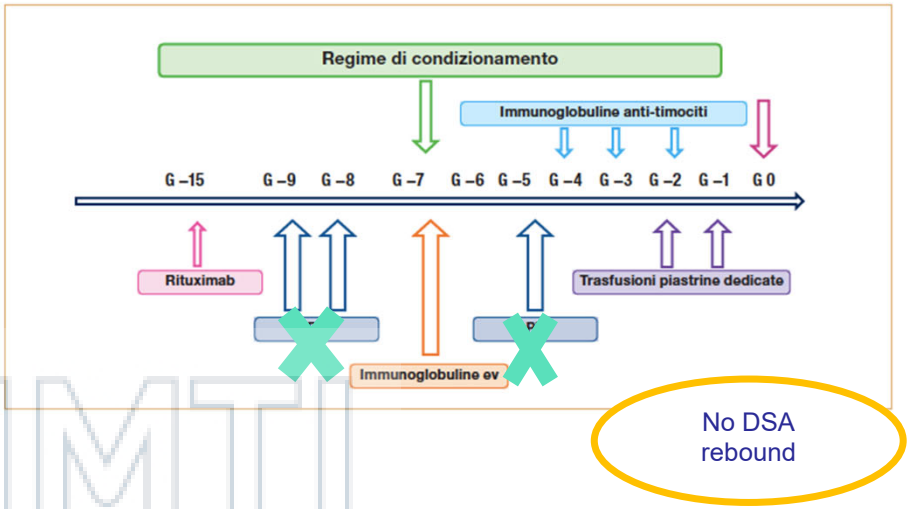
Ursula La Rocca[1], Maria P. Perrone[2], Alfonso Piciocchi[3], Walter Barberi[1], Paola Gesuiti[2], Luca Laurenti[2], Paola Cinti[2], Maria Gozzer[2], Manhaz Shafii Bafti[2], Daniela Carmini[2], Nadia Cinelli[2], Claudio Cavallari[2], Gianluca Giovannetti[2], Roberto Ricci[2], Gabriella Girelli[2], Robin Foà[1], Maurizio Martelli[1], Serelina Coluzzi[2], Anna P. Iori[1]

126 pts candidates for **MM HSCT**
Median Age: 48 yrs (5-69 yrs)

Anti-HLA Abs:
22 pts (17.46%)
DSAs: 5 pts (3.9%)

85 patients underwent **HSCT**

4 DSAs



Anti-HLA antibodies

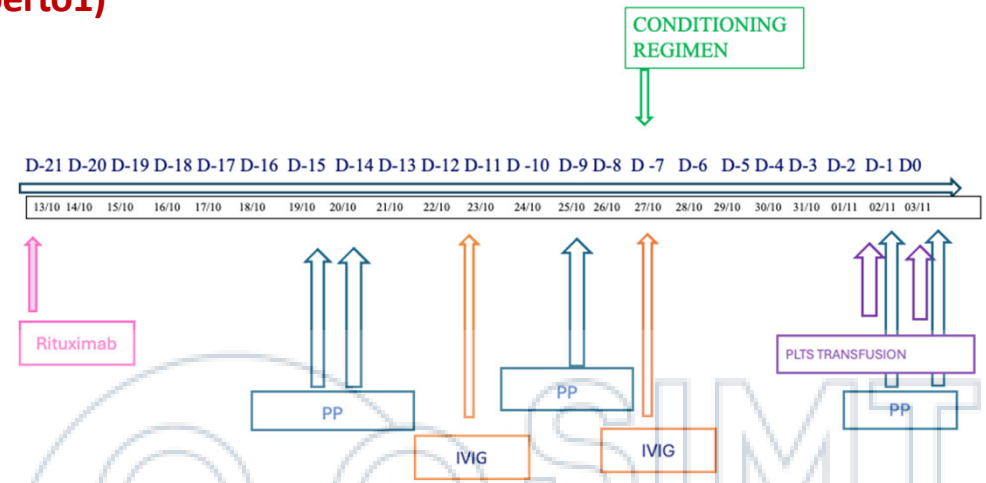
Characteristic	p-value[1]
Age, median (range)	0.56
Gender, n (%)	**0.033**
Pregnancies/ n (%)	**0.009**
Pre-HSCT Blood Transfusions n (%)	0.39
RBC Transfusions, median (range)	0.69
PLT Transfusions, median (range)	0.87
Plasma Transfusions, median (range)	0.72

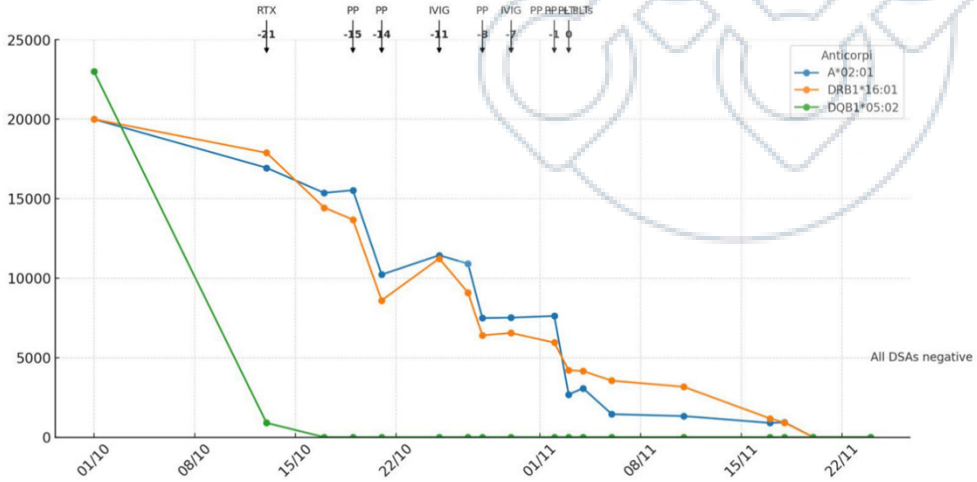
GENDER	DONOR	CLASS I DSA MFI	CLASS II DSA MFI	XM	DS	CD34+ X 10^6/Kg	PMNE	PLTSE	CHIMERISM D+20	GF	PGF	A-GVHD	F-UP
FEMALE	HAPLO	CW6 1667		N	DS	3,82	17	25	100,00%	0	0	II	ALIV
MALE	HAPLO	A2 1109		N	not applied (DSA-Pre-CR)	2,49	18	27	100,00%	0	0	II	ALIV
FEMALE	HAPLO		DR7 1200	N	DS	0,58	18	27	100,00%	0	0	0	ALIV
FEMALE	HAPLO	A2 2263		N	DS	2,39	15	64	100,00%	0	0	II	ALIV

La Rocca et al. Blood Transfus. 2024

CASO CLINICO (Policlinico Umberto1)

- Donna, 59 anni, LMA FLT3-NPM1 positiva
- Remissione completa dopo induzione + consolidamento
- HSCT aploidentico (figlio), Nessun donatore alternativo





⚠️ DSA
- A02:01 → **MFI 20.347**
- DRB1*16:01 → **MFI 20.559**
- DQB1*05:02 → **MFI 1.658**
- Alto rischio di GF

💊 Desensibilizzazione
- Rituximab (−21)
- Plasmaferesi ×5
- IVIG
- Piastrine HLA-selezionate
- Riduzione progressiva DSA
  Negativizzazione entro giorno +14

🌱 Engraftment
- Neutrofili: giorno +23
- Piastrine: giorno +60
- Nessun rebound anticorpale

⚠️ Complicanze
- GVHD acuta grado I → steroidi
- Riattivazione CMV (5 mesi)
- Citopenie transitorie

✅ Follow-up (25 mesi)
- Trasfusione-indipendente
- Remissione molecolare
- Chimerismo completo stabile

Faccini A, et al. 2026 Submitted

STUDIO GITMO AIBT DSA

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

- **Studio italiano, retrospettivo, osservazionale, multicentrico,** spontaneo, non-interventistico, non farmacologico, proposto da **GITMO** ed **AIBT** in collaborazione con l'**IBMDR**
- Coordinato dalla UOC di [illegible]matologia, Pol. Umberto 1, Università Sapienza .

- Volto a **descrivere gli approcci per la gestione dei pazienti candidati a trapianto con DSA** nella **realtà dei Centri Trapianto Italiani**, e definire una strategia comportamentale **propedeutica a studi prospettici**.

- Includente **tutti** i pazienti sottoposti a **TMO di cellule staminali emopoietiche (CSE) mismatched (mm)** tra il **2014 ed il 2017**.

2014–2017

PERIODO DI ARRUOLAMENTO

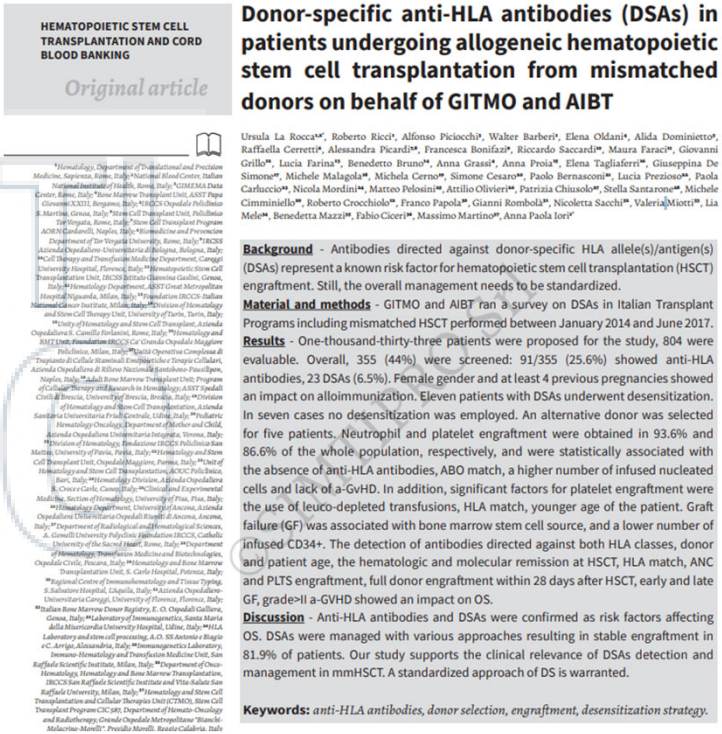
804

PAZIENTI VALUTABILI

HSCT da donatori mismatch

CLINICALTRIALS.GOV

NCT04469085



HEMATOPOIETIC STEM CELL TRANSPLANTATION AND CORD BLOOD BANKING

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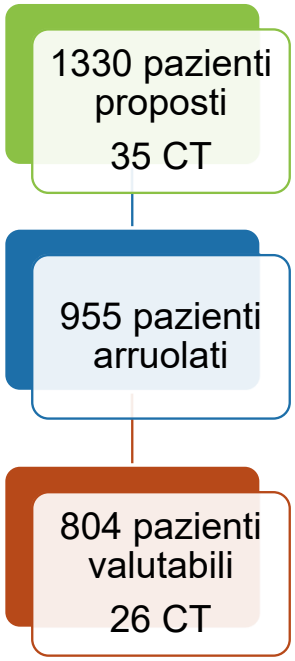
Background - Antibodies directed against donor-specific HLA allele(s)/antigen(s) (DSAs) represent a known risk factor for hematopoietic stem cell transplantation (HSCT) engraftment. Still, the overall management needs to be standardized.
Material and methods - GITMO and AIBT ran a survey on DSAs in Italian Transplant Programs including mismatched HSCT performed between January 2014 and June 2017.
Results - One-thousand-thirty-three patients were proposed for the study, 804 were evaluable. Overall, 355 (44%) were screened: 91/355 (25.6%) showed anti-HLA antibodies, 23 DSAs (6.5%). Female gender and at least 4 previous pregnancies showed an impact on alloimmunization. Eleven patients with DSAs underwent desensitization. In seven cases no desensitization was employed. An alternative donor was selected for five patients. Neutrophil and platelet engraftment were obtained in 93.6% and 86.6% of the whole population, respectively, and were statistically associated with the absence of anti-HLA antibodies, ABO match, a higher number of infused nucleated cells and lack of a-GvHD. In addition, significant factors for platelet engraftment were the use of leuco-depleted transfusions, HLA match, younger age of the patient. Graft failure (GF) was associated with bone marrow stem cell source, and a lower number of infused CD34+. The detection of antibodies directed against both HLA classes, donor and patient age, the hematologic and molecular remission at HSCT, HLA match, ANC and PLTS engraftment, full donor engraftment within 28 days after HSCT, early and late GF, grade>II a-GVHD showed an impact on OS.
Discussion - Anti-HLA antibodies and DSAs were confirmed as risk factors affecting OS. DSAs were managed with various approaches resulting in stable engraftment in 81.9% of patients. Our study supports the clinical relevance of DSAs detection and management in mmHSCT. A standardized approach of DS is warranted.

Keywords: *anti-HLA antibodies, donor selection, engraftment, desensitization strategy.*

La Rocca et al. Blood Transfus. 2025

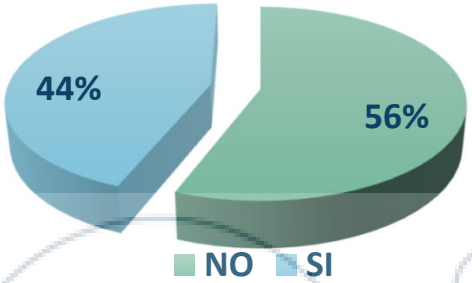
RISULTATI



CT: 26	
Totale pazienti	804
età (mediana)	48 (0, 72)
F/M	287 (36%) / 517(64%)
Gravidanze n (%)/ Aborti n (%)	127 (55%)/12 (4.9%)
Trasfusioni pre-HSCT, n(%)	630 (88%)
Trasfusioni leucodeplete, n (%)	545 (86%)
Regime di condizionamento ad intensità mieloablativa, n (%)	584 (77%)
TBI, n (%)	96 (12%)
Fonte di CS, n (%) MO/SCO/SVP	347 (43%)/42 (5.2%)/375 (47%)
Compatibilità HLA, n (%) correlati MM/Non correlati	352 (44%)/452 (56%)
MM HLA donatori correlati, n (%)	
≥2 HLA loci MM/1 HLA locus MM	341 (98%)/7 (2%)
ABO: Compatibili / I. Magg/I. Minore/ I. Bidir., n (%)	147 (25%)/ 207 (35%)/ 204 (35%)/ 27 (4.6%)
età del donatore, median (range)	33 (10, 66)
Sesso del donatore , F/M, n (%)	280 (35%)/516 (65%)

RISULTATI Ricerca anticorpi anti-HLA e DSA, policy di screening

Ricerca anticorpi anti-HLA
355/804



Risultati anti-HLA

Negative 264 (74.3%)
Positive 82 (25%)

- Classe I 42 (12%)
- Classe II 26 (7.3%)
- ntrambe 23 (6.4%)

MFI 8.300 (<500 -23.000)

Metodi utilizzati per la ricerca anticorpale:

- Luminex 335 (94.3%)
- LISA 17 (4.78%)
- lisa + Luminex 3 (0.84%)

Complement Activity valuation:

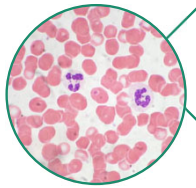
- C1q/C3d: 26 (7.6 %)

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

Variabile analizzata	Anti-HLA antibodies screening p-value[1]	Anti-HLA antibodies result p-value[1]
Genere	0.17	0.003
Gravidanze	0.028	0.89
Numero di gravidanze (≥4)	0.25	0.024
Aborti	0.95	0.077
Trasfusioni pre-HSCT	0.007	0.064

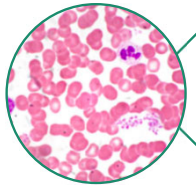
[1]Pearson's Chi-squared test

RISULTATI Attecchimento



NEUTROFILI

- **93.6%**



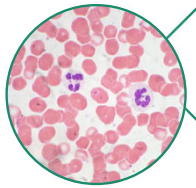
PIASTRINE

- **86.6%**

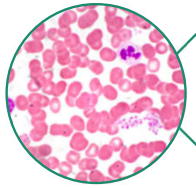
Variabili analizzate	Attecchimento PMN p-value[1]	Attecchimento PLTS 20.000 p-value[1]	Attecchimento PLTS 50.000 p-value[1]	Attecchimento completo a 28 giorni p-value[1]
Gravidanze, n (%)	0.21	>0.99	>0.99	>0.99
Aborti, n (%)	0.19	0.68	0.69	0.97
Leucodeplezione, n (%)	0.14	0.005	0.050	0.006
Compatibilità HLA, n (%)	0.13	<0.001	0.010	<0.001
Grado di mismatch HLA nei donatori correlati, n (%)	0.92	0.42	0.75	0.014
□ità del donatore, mediana (range)	0.73	0.086	0.27	0.90
Remissione ematologica pre-HSCT, n (%)	>0.99	0.56	0.006	0.88
□tà, mediana (range)	0.085	0.021	0.24	0.17
Fonte di CS□, n (%)	0.44	0.88	0.31	0.017
Regime di condizionamento MAC., n (%)	>0.99	0.69	0.93	0.009
Compatibilità ABO, n (%)	<0.001	0.002	0.18	0.004
Status CMV donatore e ricevente , n (%)	0.94	0.24	0.038	0.28
Mismatch di genere donatore e ricevente, n (%)	>0.99	0.18	0.93	0.16
Risultati anti-HLA, n (%)	0.002	<0.001	0.030	0.022
CNT totali infuse, median (range)	0.006	0.029	0.003	0.004
CD34+ infuse, median (range)	0.34	0.24	0.80	0.046
aGVHD, n (%)	0.001	0.009	0.030	0.31
aGvHD grado massimo, n (%)	0.002	<0.001	0.021	0.10

All variables analyzed: Gender, n; Number of pregnancies, n; Pre-HSCT blood transfusions, n; Anti-HLA tested before HSCT; DSA; Donor gender; TBI; Number of infused CD3 positive cells (T-cells)x10^6/kg; Cytogenetic remission; Molecular remission; Diagnosis; TBI total dose.

RISULTATI Attecchimento



NEUTROFILI
• **93.6%**



PIASTRINE
• **86.6%**

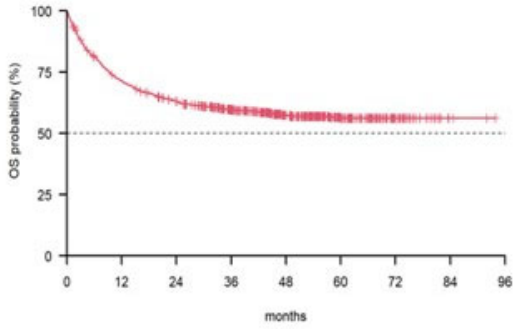
Variabili analizzate	Attecchimento PMN p-value[1]	Attecchimento PLTS 20.000 p-value[1]	Attecchimento PLTS 50.000 p-value[1]	Attecchimento completo a 28 giorni p-value[1]
Gravidanze, n (%)	0.21	>0.99	>0.99	>0.99
Aborti, n (%)	0.19	0.68	0.69	0.97
Leucodeplezione, n (%)	0.14	0.005	0.050	0.006
Compatibilità HLA, n (%)	0.13	<0.001	0.010	<0.001
Grado di mismatch HLA nei donatori correlati, n (%)	0.92	0.42	0.75	0.014
□tà del donatore, mediana (range)	0.73	0.086	0.27	0.90
Remissione ematologica pre-HSCT, n (%)	>0.99	0.56	0.006	0.88
□tà, mediana (range)	0.085	0.021	0.24	0.17
Fonte di CS□, n (%)	0.44	0.88	0.31	0.017

Early GF: 17 pz (2.7%) (35% F)
Ab anti-HLA (p=0.63)
DSA (p=0.99)

Late GF: 15 pz (2.2%) (40% F)
Ab anti-HLA (p=0.80)
DSA (p=0.60)

fonte di CSE midollari (p=0.032)
↓ CD34+ infuse (p=0.033)

RISULTATI Sopravvivenza



Variabile analizzata	HR1	95% CI1	p-value
Risultato anticorpi anti-HLA			
Negativo	0.61	0.28, 1.31	0.20
Positivo- II classe	2.80	1.65, 4.73	<0.001
Positivo-entrambe le classi	1.13	0.70, 1.85	0.61
Positivo- I classe			
Età al trapianto	1.02	1.01, 1.03	<0.001
Età del donatore	1.00	1.00, 1.00	<0.001
Remissione ematologica pre-HSCT	0.24	0.13, 0.44	<0.001
Remissione molecolare pre-HSCT	0.54	0.34, 0.88	0.013
Match HLA	0.74	0.60, 0.92	0.007
Attecchimento PLT	0.95	0.93, 0.96	<0.001
Attecchimento ANC	0.93	0.91, 0.95	<0.001
Attecchimento completo entro i 28 giorni post HSCT	0.31	0.24, 0.41	<0.001
Early graft loss	3.74	2.04, 6.88	<0.001
Late graft loss	4.18	2.33, 7.50	<0.001
a-GVHD grado > II	1.94	1.12, 3.33	0.017

1HR = Hazard ratio, CI = Confidence interval

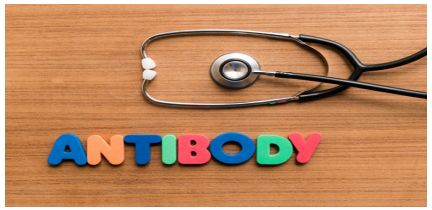
All variables analyzed: Gender; Pregnancies; Number of pregnancies; Abortions; Nr. of abortions; pre-HSCT blood transfusions, Leucodepleted blood transfusions; Anti-HLA tested before HSCT; Anti-HLA result; DSA detection; Cytogenetic remission before HSCT; ABO mismatch; donor and recipient CMV status; Patient gender; Donor gender; Gender mismatch; TBI; Stem cell source; Number of infused CD34 positive cells; Number of infused CD3 positive cells (T-cells); Full donor ngraftment within 28 day; arly Graft Loss; Late Graft Loss; aGVHD.

Follow up mediano
51.32 mesi (0.0-93.9)

OS
48 mesi: 57.4%
60 mesi 56.5%

Variabile analizzata	HR1	95% CI1	p-value
Ricerca anticorpi anti-HLA			
Positivi-entrambe le classi	2.37	1.28, 4.41	0.006
tà al trapianto	1.01	1.00, 1.03	0.020
Attecchimento completo entro i 28 gg	0.62	0.43, 0.89	0.010
Early graft loss	2.99	1.42, 6.26	0.004
1HR = Hazard ratio, CI = Confidence interval			

RISULTATI: APPROCCI ADOTTATI



23 PAZIENTI DSA+

11 pazienti

a) 7 pazienti: clearance DSA
7/7 attecchimento completo
1/7 no attecchimento PLTS

b) 2 pazienti: riduzione DSA
1/2 attecchimento completo
1/2 early graft loss

c) 2 pazienti: persistenza
1/2 attecchimento completo
1/2 graft failure

SELEZIONE DONATORE ALTERNATIVO

5 pazienti

Attecchimento completo

NO STRATEGIE

7 pazienti

4/7 attecchimento completo
3/7 No attecchiemnto PLTS

DSA: 6.5% dei pazienti sottoposti a screening

Attecchimento nell'81,9% dei pazienti

STRATEGIE DI DESENSIBILIZZAZIONE IMPIEGATE

	Rituximab (375 mg/m2) on day -15, plasmapheresis (PP) on days -9 and -8, intravenous immunoglobulin (IVIG) on day -7. Selected platelet transfusions were employed in the case of antibodies directed against class I HLA.
	PP procedures on days -10, -8, and -1.
	PP procedures using EC30 W filters (days not specified).
	Weekly PP procedures and rituximab 375 mg/m2 (repeated for four weeks) were administered.
	Rituximab 375 mg/m2/week for 4 weeks and IVIG 1 g/kg/day for 2 consecutive days were administered, followed by the infusion of donor-irradiated PLT transfusions.
	Rituximab 375 mg/m2 on day -7.
	IVIG followed by selected platelet transfusion in patients with antibodies directed against class I HLA.
	PP procedures on two consecutive days followed by IVIG.

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

AIBT
Associazione Italiana di Immunogenetica e Biologia dei trapianti

RACCOMANDAZIONI AIBT PER LA VALUTAZIONE DELLA ISTOCOMPATIBILITA' NEL TRAPIANTO DI CELLULE STAMINALI EMOPOIETICHE
(Versione 1.0 del 2 Dicembre 2021)

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Crocchiolo, Roberto
Falco,Michela
Fusco,Caterina
Garbarino,Lucia
Papola,Franco
Rombolà,Gianni
Vecchiato,Cinzia

4.1 Ricerca anticorpi anti-HLA donatore specifici

Nel ricevente di CSE non può essere esclusa la presenza di anticorpi anti-HLA nel paziente, in particolare quelli specificamente diretti nei confronti del donatore (DSA), a causa di immunizzazioni pregresse. In presenza di mismatch nella coppia donatore-ricevente si deve pertanto eseguire (*must*) lo screening degli anticorpi anti-HLA, in particolare nel trapianto aploidentico caratterizzato dalla presenza di numerosi mismatch tra donatore e ricevente per la presenza di un intero aplotipo HLA non condiviso.

Un recente studio multicentrico indica che, in una analisi multivariata, fattori indipendenti di rischio di formazione di anticorpi nel ricevente in attesa trapianto di CSE siano, oltre che il numero delle gravidanze e delle trasfusioni, anche il sesso femminile e la patologia di base (sindrome mielodisplastica) (*Huo MR et al, Hum Imm 2018*). È pertanto rilevante eseguire nel caso di trapianto aploidentico la ricerca di anticorpi anti-HLA nel ricevente, per permettere al clinico una scelta tra i possibili donatori aploidentici e ripetere la ricerca al momento del work up per una definizione del rischio clinico e l'eventuale desensibilizzazione. La ricerca deve essere estesa ad anticorpi diretti contro tutte le specificità HLA di I e II classe.

La tecnica di riferimento per la ricerca degli anticorpi è la Beads Based Immunoassay (Luminex) che permette di identificare le singole specificità HLA e l'ampiezza o spettro di immunizzazione (PRA), eventualmente integrata con altre tecniche (CDC, C1q/C3d, CDC-XM, FCXM). La ricerca degli anticorpi anti-HLA dovrebbe essere effettuata anche in altre tipologie di trapianto da donatore non HLA identico (CSE da cordone ombelicale, Mis-Matched Unrelated Donor - M-MUD) (*Dehn J et al, Blood 2019*) ed è preferibile eseguirla nelle fasi iniziali della ricerca del donatore, in virtù dell'opportunità, laddove possibile, di cambiare il donatore in caso di presenza di DSA; inoltre, se nel ricevente fossero presenti anticorpi diretti contro epitopi espressi da loci che non sono stati tipizzati nel donatore (per es. DQA1, DPA1), sarebbe indicata la tipizzazione di questi loci per discriminare tra DSA o non DSA (vedi allegato A).

- **Screening anti-HLA sempre necessario (must), soprattutto nel trapianto aploidentico**
- **Identifica DSA → impatto su scelta del donatore e rischio immunologico**
- **Fattori di rischio: gravidanze, trasfusioni, sesso femminile, MDS**
- **Tecnica di riferimento: Luminex (SAB) ± test funzionali**
- **Da eseguire precocemente → possibile cambio donatore**
- **Estendere a tutte le specificità HLA (classe I e II)**

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

Buffy Coat

Complessità della gestione trasfusionale nei pazienti alloimmunizzati.

Comparison of methods used to identify compatible platelet units for alloimmunized patients

	Crossmatched	HLA matched	HLA compatible
Method	Test patient's serum against a panel of platelets to determine compatibility	Identify platelet donors with perfect (4/4) match for patient's HLA class IA and IB alleles	ASP: Use antibody specificities to select donor units that lack corresponding antigens
Pros	• Rapid turnaround-time	• 4/4 match ensures HLA compatibility	• Larger donor pool
	• Obtain compatible units without HLA genotype or HLA antibody testing	• Reduced risk of future alloimmunization	• Reduced risk of future alloimmunization
	• Compatible with HLA and HPA antibodies		
Cons	• Difficult to find compatible units for highly alloimmunized patients	• HLA genotyping required	• Not useful for HPA antibodies
	• Risk of alloimmunization for mismatched HLA antigens	• Limited donor pool for some patients	• HLA antibody testing required

1. C.S. Cohn et al., Hematology Am Soc Hematol Educ Program. 2020 Dec 4;2020(1):527-532.
J. Juskewitch et al., Transfusion. 2017 Dec;57(12):2828-2835

GESTIONE DELLA REFRATTARIETÀ IMMUNOLOGICA

Algoritmo sviluppato da R. Duquesnoy che consente di predire le regioni sugli epitopi conformazionali (T?RTIARY STRUCTUR?) delle molecole HLA (eplets HLA) sono accessibili agli alloanticorpi riducendo il numero di donatori tipizzati necessari per gestire i pazienti refrattari

Epitope-matched platelets for HLA-alloimmunized patients		
A noninferiority, cross-over, randomized trial		
Overall, 49 patients with aplastic anemia, MDS or AML, who were alloimmunized, platelet refractory, and thrombocytopenic, were randomized and analyzed	Post transfusion platelet count increment with HLA epitope-matched (HEM) platelets (107 transfusions) **23.9±15.0**	Post transfusion platelet count increment with HLA standard antigen-matched (HSM) platelets (112 transfusions) **23.5±14.1**
Epitope-matched platelets were not inferior		
There were no differences in secondary outcomes of platelet counts, transfusion requirements, and bleeding events		
HEM platelets are available for sensitized patients who might not be classed as matched using standard antigen matching		

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

Disponibili approcci avanzati per la gestione della refrattarietà, con il matching a livello di epitopi.
Attraverso **algoritmi come HLA Match maker è possibile identificare gli eplets,** cioè le porzioni strutturali delle molecole HLA realmente riconosciute dagli anticorpi, superando il semplice matching antigenico.
Questo consente di **ampliare il pool di donatori compatibili e migliorare la gestione dei pazienti alloimmunizzati**.

Marsh, Stanworth, et al. An epitope-based approach of HLA-matched platelets for transfusion: a noninferiority crossover randomized trial, Blood, 2021

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Received: 29 December 2019 | Revised: 8 February 2020 | Accepted: 13 February 2020
DOI: 10.1002/ajh.25762

Donor-specific anti-HLA antibodies and ...recipient-specific anti-HLA antibodies? The conundrum on pregnancy in transplantation

To the Editor:
The presence of Donor-Specific anti-HLA Antibodies (DSA) in recipients has been associated with increasing risk of graft failure in hema-

Ciurea SO, et al. Am J Hematol. 2020.

Recipient-specific antibodies in HSCT: current knowledge and future perspectives

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Pasi A, et al. Front. Immunol. 2025

Gli RSA rappresentano un aspetto ancora poco esplorato ma potenzialmente rilevante dell'immunologia del trapianto.
A differenza dei DSA, più chiaramente associati a graft failure, **gli RSA sembrano avere un ruolo distinto, soprattutto nella modulazione immunitaria e nello sviluppo di GVHD e danno endoteliale.**

La gestione del paziente positivo a DSA nel trapianto allogenico di CSE

In addition to measuring DSAs in the recipient's serum, antibodies against recipient HLA antigens (RSAs)should probably be tested in adult female donors considered for haploidentical transplantation as part of the routine pre-transplant work-up.

CONCLUSIONI

È essenziale escludere la **presenza di alloimmunizzazione anti-HLA, in particolare DSA, prima del trapianto, mediante indagine eseguita entro 30 giorni,** al fine di garantire una **corretta gestione nelle fasi pre-, peri- e post-TMO.**

Una migliore definizione **patogenetica**, in relazione alle **specificità anticorpali ed all'espressione e densità cellulare antigene-specifica** potrebbe consentire **la definizione di nuovi, specifici target terapeutici per la desensibilizzazione anticorpale.**

Necessità di **studi prospettici multicentrici**, volti a un **miglior inquadramento** delle risposte **ai quesiti ancora aperti**, quali l'armonizzazione delle strategie diagnostiche, il **rischio immunologico,** tenendo conto delle **altre variabili (diagnosi, regime di condizionamento e profilassi della GVHD, cut-off MFI),** e la **miglior strategia desensibilizzante** in relazione ai **valori di MFI.**

È necessaria una **forte collaborazione** tra medici **trapiantologi, trasfusionisti e immunogenetisti per la definizione di schemi di gestione e desensibilizzazione** laddove **l'urgenza trapiantologica** e le **caratteristiche** della coppia donatore/ricevente **prevalgano** sulla **possibilità di selezionare un donatore alternativo**.

CONCLUSIONI

BOX 1. BASIC AND ANSWERABLE QUESTIONS REGARDING DSA DESENSITIZATION IN PATIENTS WHO UNDERWENT HLA-MISMATCHED ALLOGENEIC TRANSPLANTATION

- How can the underlying mechanism be elucidated in transplant recipients who have no anti-HLA antibodies including those with several risk factors, such as pregnancy and transfusion?
- What is the role of C1q binding to DSAs in other transplant modalities, except for in patients who receive haploidentical allografts?
- What are the effects of non-DSAs pre-HSCT on transplant outcomes?
- What are the kinetics of DSAs and non-DSAs after HLA-mismatched allograft transplantation and their association with transplant outcomes?
- What is the optimal cutoff value for the DSA level for desensitization? Are there different DSA cutoff values for desensitization among different transplant modalities?
- What is the optimal combination of different desensitization strategies for patients with high levels of DSAs?
- How can individualized desensitization therapy be administered according to the individual's DSA level?
- Which biomarkers could predict the effectiveness of DSA desensitization strategies?

Zhou et al. 2024

There is a need for prospective multicentric studies to define the role of DSAs in relation to each HLA loci, the MFI cutoff associated with a higher risk of graft rejection, and the efficacy of a desensitization strategy.

Anticorpi anti-HLA donatore-specifici (DSAs) nei pazienti candidati a trapianto allogenico mismatched

Codice Identificativo dello Studio: GITMO - AIBT DSAs

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279	Bonanomi Sonia	Monza	CTMO Fond MBBM Clinica pediatrica
286	Bernasconi Paolo	Pavia	Policlinico S. Matteo
287	Proia Anna	Roma	San Camillo Forlanini
294	Grillo Giovanni	Milano	Niguarda
304	Donnini Irene	Firenze	AOU Careggi
305,2	Aglietta Massimo	Candiolo	FPO IRCCS Candiolo
307	Chiusolo Patrizia	Roma	Policlinico Gemelli
341	De Simone Giuseppina	Napoli	Azienda ospedaliera Santobono Pausilipon
354	Bramanti Stefania	Milano	Humanitas
526	Carella Angelo Michele	S. Giovanni Rotondo	Casa Sollievo della Sofferenza
557	Zecca Marco	Pavia	Policlinico S. Matteo
587	Martino Massimo	Reggio Calabria	A. Neri Bianche Melacrino Morelli
606	Mordini Nicola	Cuneo	ASO S. Croce e Carle
616	Farina Lucia	Milano	IST
649	Paola Carluccio	Bari	Policlinico di Bari
652	Pavone Vincenzo	Tricase	Osp. Card. Panico
658	Grassi Anna	Bergamo	H Papa Giovanni XXIII
705	Cerno Michela	Udine	Ospedale Santa Maria della Misericordia
756	Picardi Alessandra	Roma	Università Tor Vergata
788	Olivieri Attilio	Ancona	Ospedali Riuniti
795	Pelosini Matteo	Pisa	A.O.U. Pisana ematologia
813	Ciceri Fabio	Milano	Ospedale San Raffaele
861	Cimminiello Michele	Potenza	Ospedale San Carlo
623.1	Andreini Angelo	Verona	Policlinico GB Rossi
623.2	Cesaro Simone	Verona	A.O.U. Integrata Verona oncoematologia pediatrica

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