Graft Manipulation : Indication and techniques

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Medanta The Medicity

Gurgaon

Disclosure

- Nothing to declare

What we will discuss?

- Graft manipulation & indications
- Haplo Platforms – T cell Replete and deplete
- T cells
- TCR alpha beta/CD19 Depletion
- Indications
- PID
- Thalassemia
- Leukemia
- Inborn Error of Metabolism
- CD45 RA Memory Add back
- Summary

What is Graft Manipulation?

Ex Vivo Optimization

Graft manipulation refers to the *ex vivo* (outside the body) processing of the stem cell product—whether bone marrow, peripheral blood, or cord blood—prior to infusion.

Primary Goals

- **Reduce GVHD:** Eliminating alloreactive T-cells.
- **Improve Engraftment:** Concentrating stem cells.
- **Safety:** Removing incompatible RBCs or reducing volume.

Key Indications

HLA Mismatch

Crucial for **Haploidentical** transplants to prevent severe reaction from mismatched antigens.

High GVHD Risk

For patients unable to tolerate standard immunosuppression or those at high risk of chronic complications.

ABO Incompatibility

Prevention of acute hemolysis in major blood group mismatches (e.g., Donor A to Recipient O).

Volume Reduction

Essential for small pediatric recipients to prevent fluid overload during infusion.

Categories of Manipulation

Physical Techniques

Basic processing methods primarily for safety and storage.

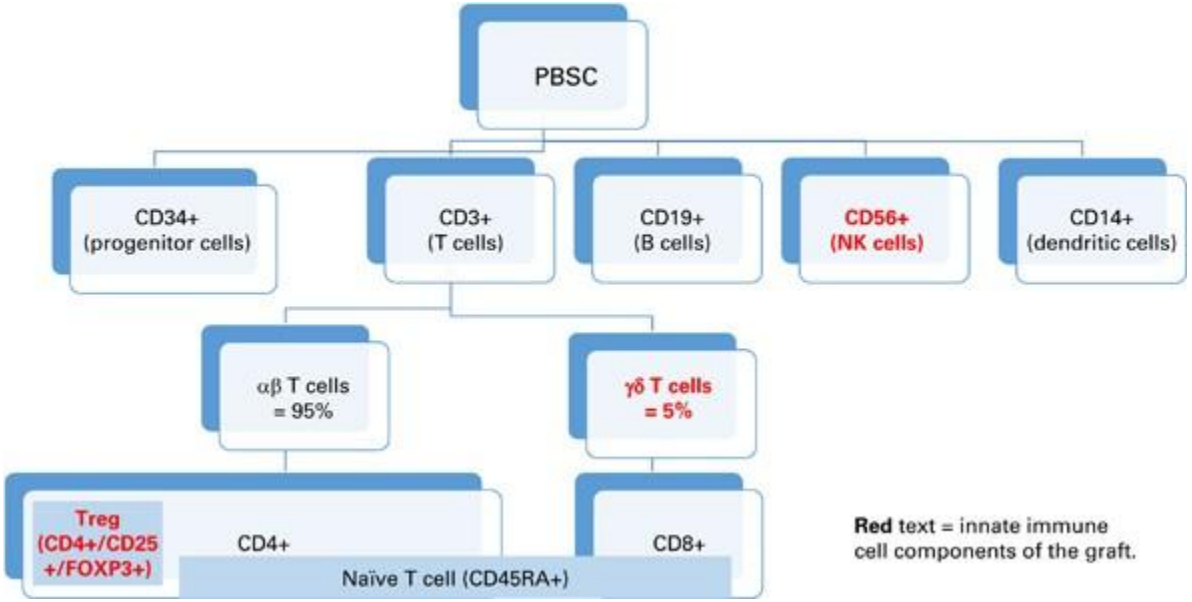
- **Centrifugation:** Volume reduction.
- **Washing:** Removal of plasma/antibodies.
- **Density Gradient:** Red blood cell depletion (e.g., Ficoll).

Immunological Techniques

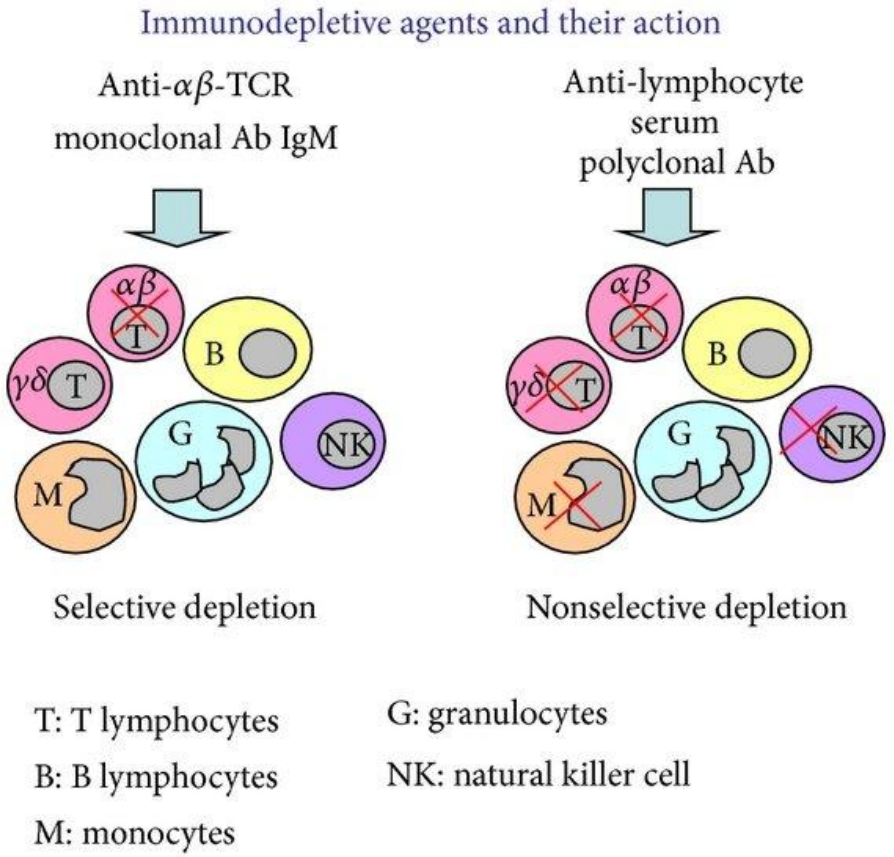
Sophisticated selection using monoclonal antibodies and magnetic beads.

- **Positive Selection:** Keeping what you want (e.g., $CD34^+$).
- **Negative Selection:** Removing what you don't want (e.g., $CD3^+$, $TCR - \alpha\beta$).

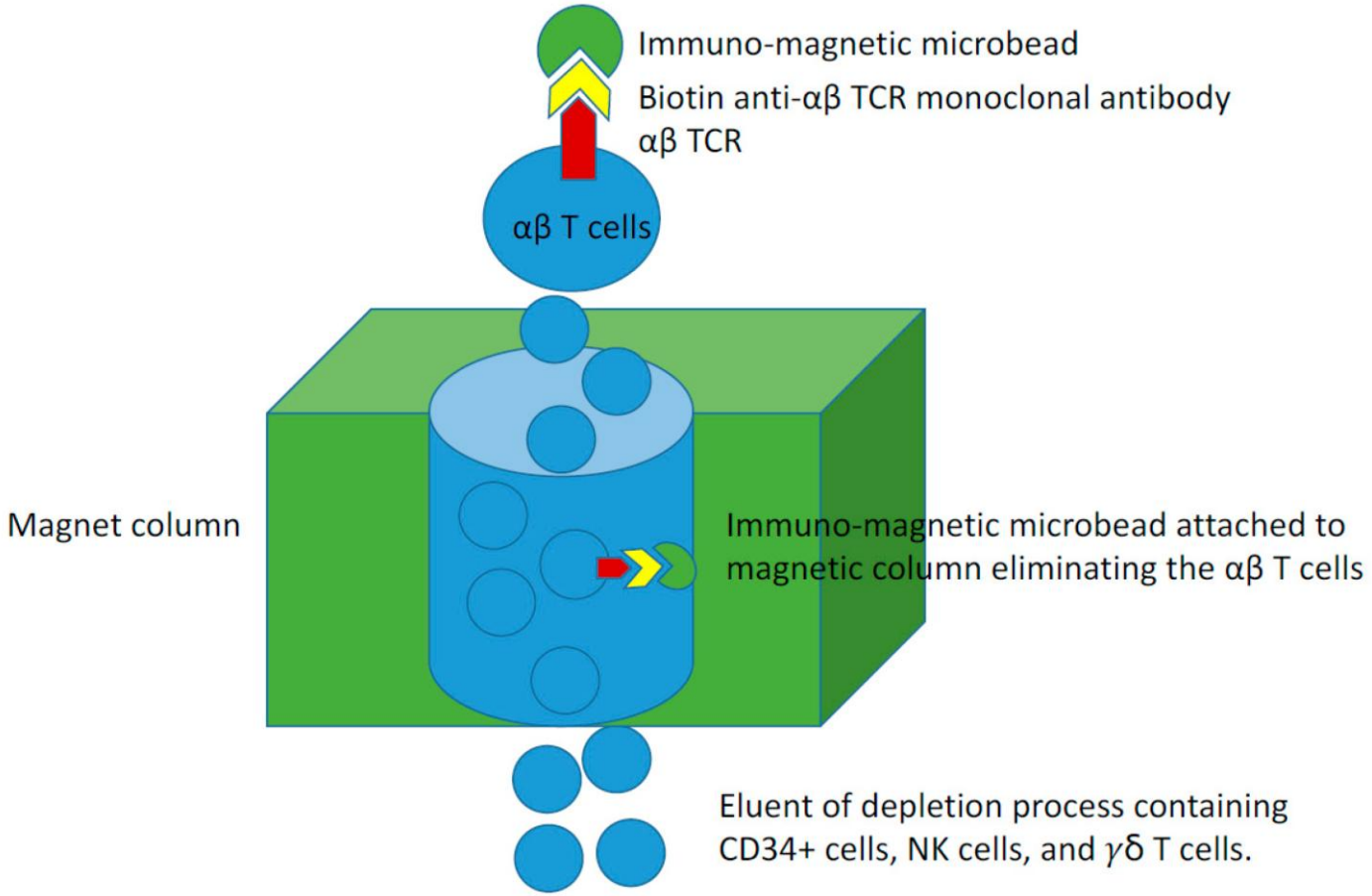
Donor cells


PBSC
CD34+ (progenitor cells)
CD3+ (T cells)
CD19+ (B cells)
CD56+ (NK cells)
CD14+ (dendritic cells)
αβ T cells = 95%
γδ T cells = 5%
Treg (CD4+/CD25 +/FOXP3+)
CD4+
CD8+
Naïve T cell (CD45RA+)
Red text = innate immune cell components of the graft.

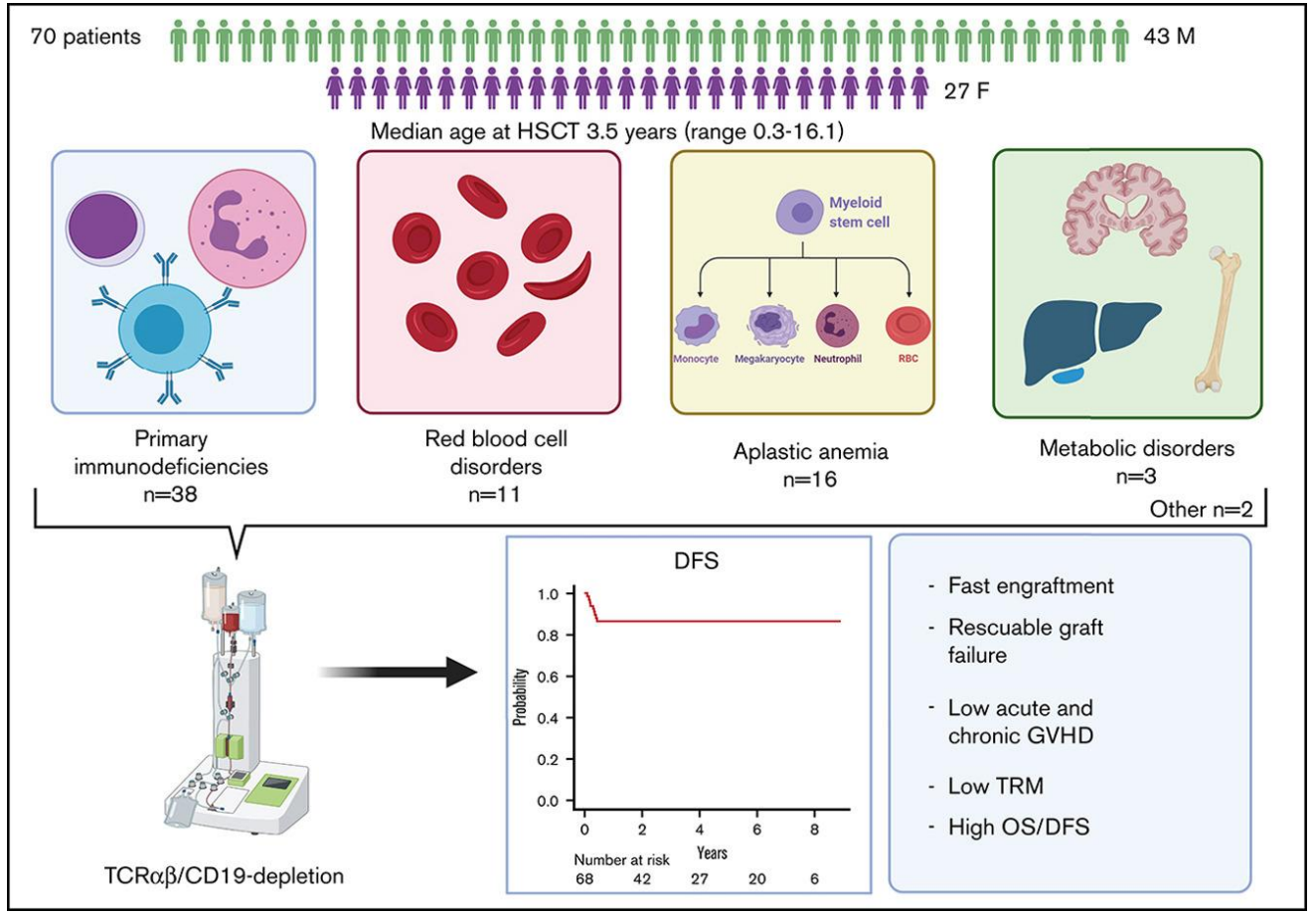
T cell Depletion



TCR alpha beta depletion



TCRαβ/CD19 depleted HSCT from an HLA-haploidentical relative to treat children with different nonmalignant disorders



P Merli, D Pagliara, F Galaverna, *et al.* Blood Adv, 6 (1) (2022), pp. 281-292

TCRαβ/CD19 Cell-Depleted HLA-Haploidentical Hematopoietic Stem Cell Transplantation (HSCT) in Pediatric Acute Leukemia (AL)

TCRαβ/CD19 cell-depleted HLA-haploidentical HSCT transplantation

✗ TCRαβ+ cells

✓ TCRγδ+ cells

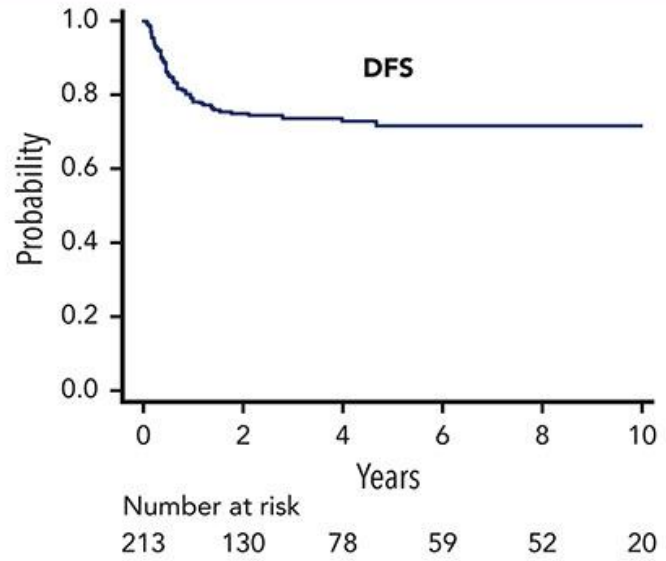
✗ CD19+ cells

✓ NK cells

Haplo-HSCT after αβ T- and B-cell depletion represents a competitive alternative for children with AL in need of urgent allograft (*Blood. 2017 Aug 3;130:677-685*)

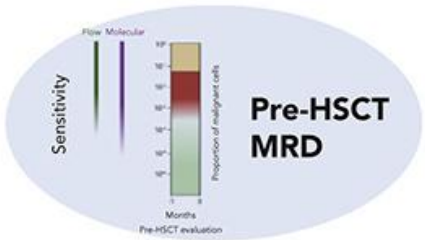
Clinical study:

- 213 children/young adults
- Median age 9.5 years
- 152 ALL / 61 AML
- All in CR at HSCT
- Median follow-up 47.6 months



Variables associated with outcome:

TBI



Pre-HSCT MRD

CR1, CR2 Disease

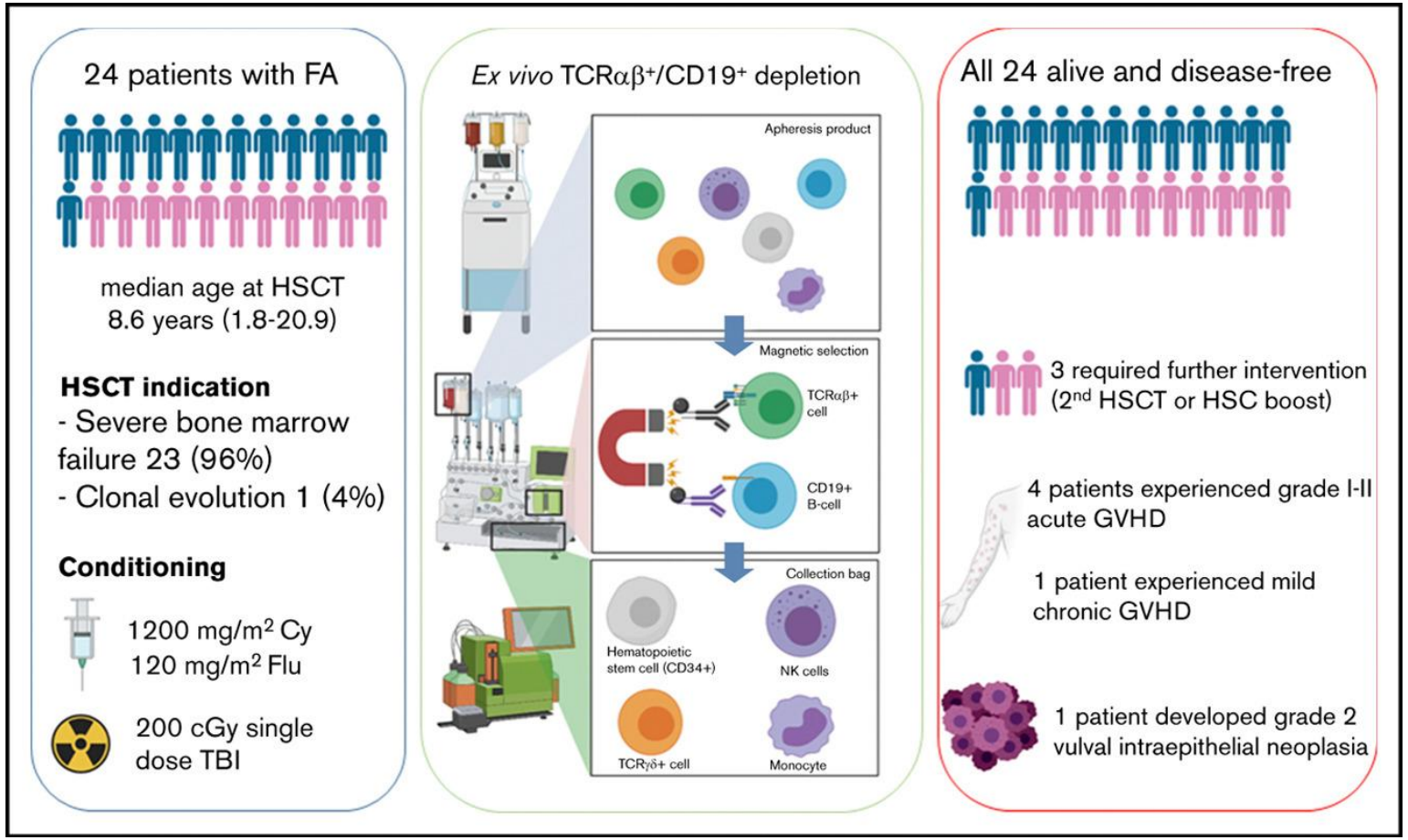
CR3, CR4 phase

Conclusions: 1) The outcomes of pediatric patients with acute leukemia given TCRαβ/CD19-depleted HLA-haploidentical HSCT are almost superimposable on those of transplant from HLA-matched donors; 2) use of TBI, low/negative levels of MRD, and transplant in CR1/2 are associated with improved outcome.

*Merli et al. DOI: 10.1182/**blood**.2023021336*

***Blood* Visual Abstract**

HLA-haploidentical TCRαβ⁺/CD19⁺-depleted stem cell transplantation in children and young adults with Fanconi anemia



L Strocchio, D Pagliara, M Algeri, *et al.* Blood Adv, 5 (5) (2021), pp. 1333-1339

Haplo – T depleted

- Initially difficult transplants
- Newer platforms
- TCR alpha beta
- BPX 501

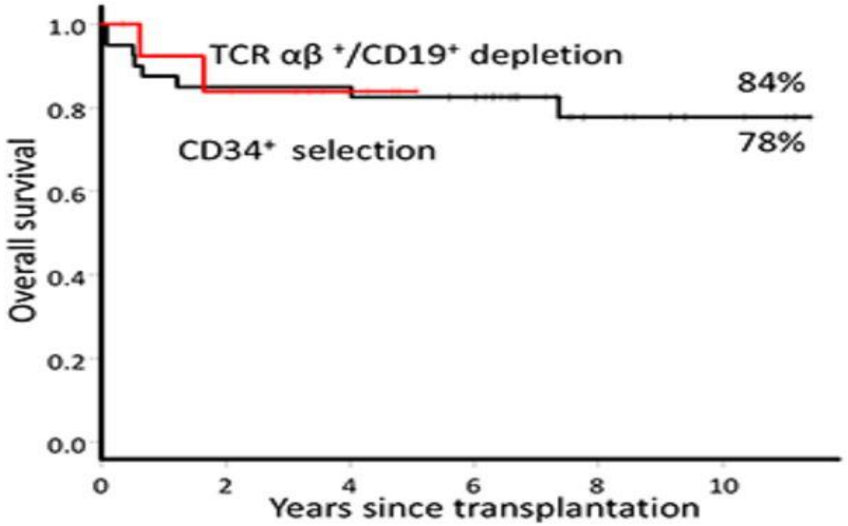
REGULAR ARTICLE

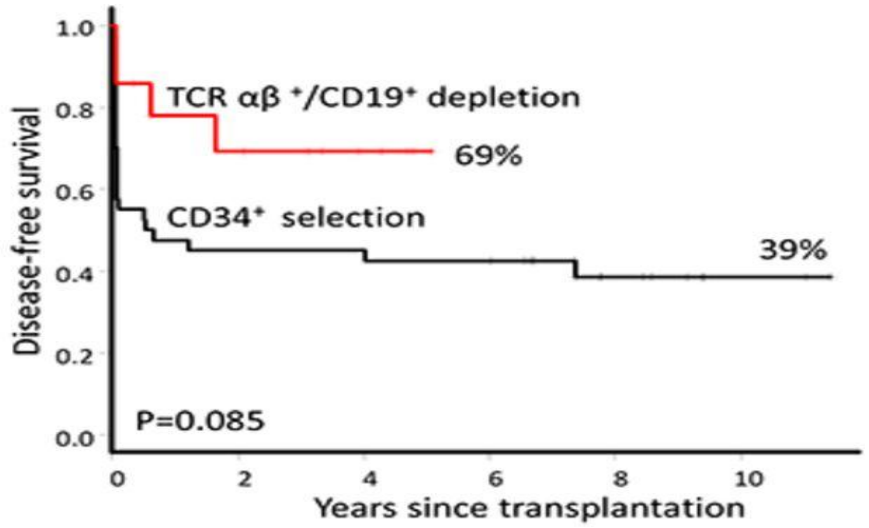
blood advances

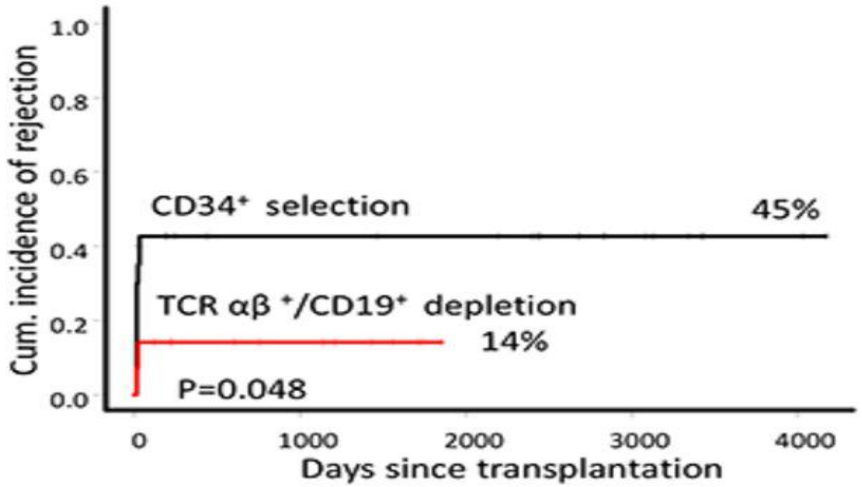
Haploidentical HSCT for hemoglobinopathies: improved outcomes with TCR$\alpha\beta^+$/CD19$^+$-depleted grafts

Javid Gaziev,[1] Antonella Isgrò,[1] Pietro Sodani,[2] Katia Paciaroni,[1] Gioia De Angelis,[1] Marco Marziali,[1] Michela Ribersani,[1] Cecilia Alfieri,[1] Alessandro Lanti,[3] Tiziana Galluccio,[1] Gaspare Adorno,[3] and Marco Andreani[1]

[1]International Center for Transplantation in Thalassemia and Sickle Cell Anemia, Mediterranean Institute of Hematology, Policlinico Tor Vergata, Rome, Italy; [2]Unità Operativa Complessa Internal Medicine and Hematology, Azienda Ospedaliera Ospedali Riuniti Marche Nord, Ospedale Santo Croce, Fano, Italy; and [3]Servizio di Immunoematologia e Medicina Trasfusionale, Policlinico Tor Vergata Foundation, Rome, Italy







Javid Gaziev et al. Blood Adv 2018;2:263-270

Administration of BPX-501 Following TCR alpha-beta T-Cell Depleted Haplo-HSCT in Children with Thalassemia

- BPX-501 are allo T cells modified to express the inducible caspase-9 (iC9) safety switch
- BPX-501 lymphocytes provides broad virus & tumor-specific immunity
- The safety switch provides the unique ability to resolve GvHD following the administration of rimiducid
- It induces dimerization & activation of iC9, inducing apoptosis of BPX-501

Blood 2018 132:166; doi: https://doi.org/10.1182/blood-2018-166

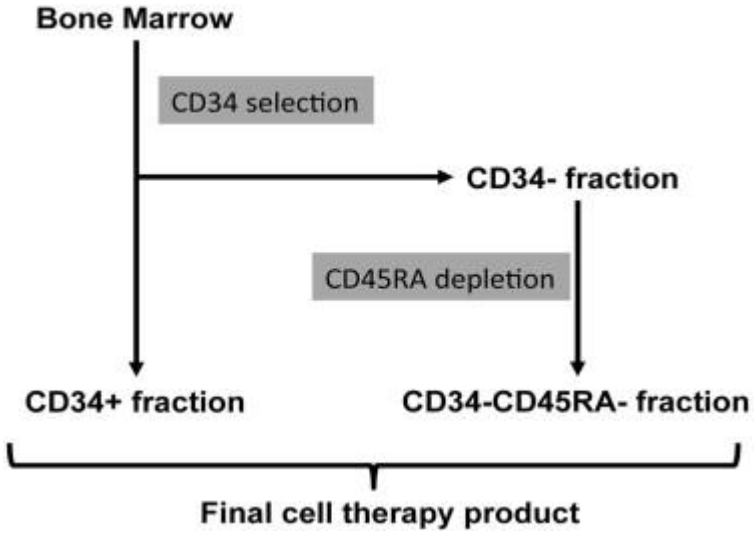
Methods

- TCR αβ/CD19 depleted haplo-HSCT was followed by infusion of donor lymphocytes BPX-501 in patients
- No post-transplant GvHD prophylaxis was employed
- 24 patients of Thalassemia median age 9 yrs (2- 14 yrs)
- Median follow-up -11.3 months
- Majority received a Bu-based conditioning regimen
- Median $CD34^+$ dose-20 million/kg and $\alpha\beta\text{-}TCR^+$ cell dose-15,000/kg
- Haplo donor was a parent in all children
- Median time to BPX-501 infusion was 17 days

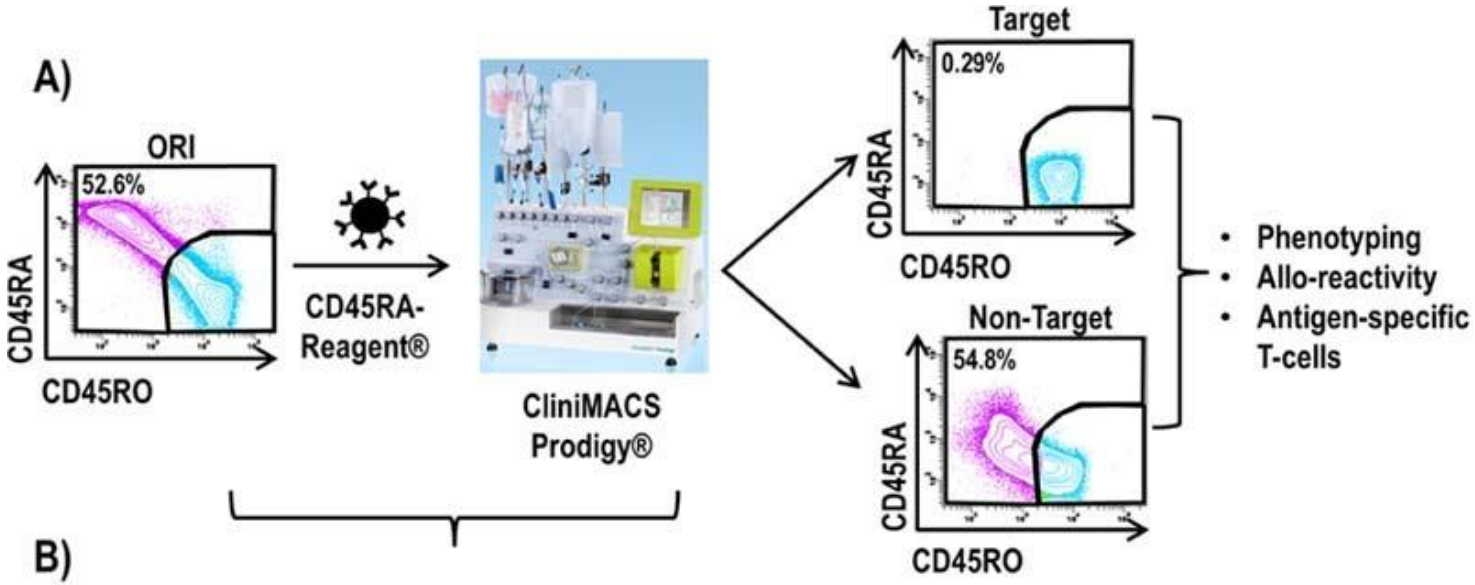
Results

- Primary graft failure seen in 2/24 (8.7%)
- One patient underwent a 2nd HSCT and remains disease free at 31 months
- 22 engrafted - median time for neutrophil -15 days & platelet-12 days
- 3 patients developed Grade 1-2 Acute GvHD & none had chronic GVHD
- Rimiducid was administered in one patient with Grade 2 Skin aGvHD who subsequently achieved a CR
- Two patients died from infections
- DFS- 82.2% & OS -90.7%
- $CD3^+$ & $CD4^+$ T cells >500 cells/ml were achieved by 180 & 270 days

CD45A depletion



Generation of alloreactivity-reduced donor lymphocyte products retaining memory function by fully automatic depletion of CD45RA-positive cells



Randomized Controlled Trial > Bone Marrow Transplant. 2021 Jul;56(7):1614-1624.
doi: 10.1038/s41409-021-01232-x. Epub 2021 Feb 16.

Safety and efficacy of the low-dose memory (CD45RA-depleted) donor lymphocyte infusion in recipients of αβ T cell-depleted haploidentical grafts: results of a prospective randomized trial in high-risk childhood leukemia

Maria Dunaikina [1], Zhanna Zhekhovtsova [1], Larisa Shelikhova [1], Svetlana Glushkova [2], Ruslan Nikolaev [3], Sergey Blagov [1], Rimma Khismatullina [1], Dmitriy Balashov [1], Elena Kurnikova [4], Dmitriy Pershin [2], Yakov Muzalevskii [4], Alexei Kazachenok [4], Elena Osipova [3], Natalia Miakova [5], Dmitriy Litvinov [5], Galina Novichkova [5], Alexei Maschan [1], Michael Maschan [6 7]

Affiliations + expand

PMID: 33594278 DOI: 10.1038/s41409-021-01232-x

Abstract

Depletion of αβ T cells from the graft prevents graft-vs.-host disease (GVHD) and improves outcome of HSCT from haploidentical donors. In a randomized trial, we aimed to evaluate the safety and efficacy of low-dose memory (CD45RA-depleted) donor lymphocytes (mDLI) after HSCT with αβ T-cell depletion. A cohort of 149 children was enrolled, 76 were randomized to receive scheduled mDLI and 73 received standard care. Conditioning was based on either 12 Gy total body irradiation or treosulfan. Rabbit antithymocyte globulin was replaced by tocilizumab and abatacept. Primary end points were the incidence of acute GVHD grades II-IV and the incidence of cytomegalovirus (CMV) viremia. The incidence of grades II-IV aGVHD was 14% in the experimental arm and 12% in the control arm, p-0.8. The incidence of CMV viremia was 45% in the experimental arm and 55% in the control arm, p-0.4. Overall, in the total cohort 2-year NRM was 2%, cumulative incidence of relapse was 25%, event-free survival 71%, and overall survival 80%, without difference between the study arms. Memory DLI was associated with improved recovery of CMV-specific T-cell responses in a subcohort of CMV

Conclusion

- T cell depletion is available and effective in reducing GVHD
- TCR alpha beta/CD19 depleted haplo outcomes are good
- Cost is a barrier to access
- Viral reactivation still a problem
- CD45 RA depletion feasible
- CD45 RA depleted donor lymphocyte infusion add back is feasible

THANK YOU