Post–allogeneic stem cell transplantation engraftment syndromes; Clinical features and Treatment

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Tehran University of Medical Sciences

The 12th international annual congress in hematopoietic stem cell transplantation

Post-alloSCT engraftment syndromes

- Graft rejection (<5% donor chimerism)
- Mixed chimerism
- Poor graft function (PGF) (>95% donor chimerism)

Poor graft function (PGF)

- At least two hematopoietic cell count lines that do not meet the engraftment standard (ANC > 1.5 x 109/L, PLT count > 30 x 109/L, Hb > 85g/L)
- At least 3 consecutive days lasting for more than two consecutive weeks beyond day +28
- Hypocellular bone marrow
- **Full donor chimerism (>95%)**
- Without severe graft-versus-host disease(GVHD), drug-induced myelosuppression, infection or disease relapse
- Frequent dependence on blood and/or platelet transfusions and/or growth factor support

Poor graft function (PGF)

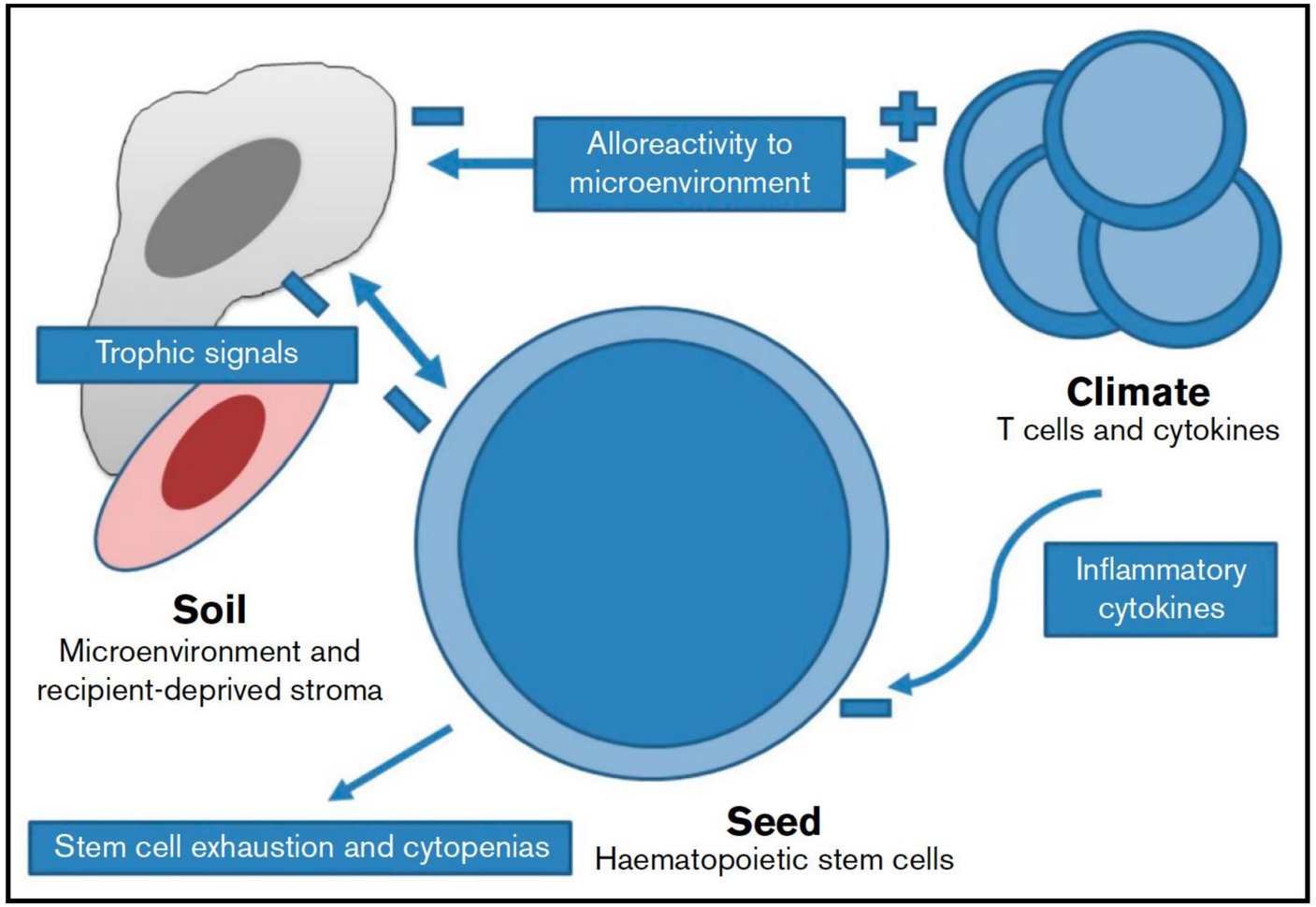
The incidence of PGF is approximately **5–27%** and has become a growing obstacle after allo-HSCT due to the development of haploidentical-HSCT.

- **Primary PGF (Early)** refers to incomplete engraftment (reconstitution).
- **Secondary PGF (Late)** is defined as a loss of initial engraftment (reconstitution).

Patients with primary PGF have a lower response rate to treatment and poorer prognosis compared with those with secondary PGF.

Survival rate is significantly lower than patients with good graft function (GGF).

Seed, soil, and climate model of Poor graft function (PGF)



Cell type/Proposed mechanism
HSC (seed)
Acquired HSC dysfunction
Reduced number of infused HSC
Loss of bone marrow microenvironment regulation by critical HSC progeny such as megakaryocytes and neutrophils
Nonhematopoietic stromal cells/bone marrow microenvironment (soil)
Loss of stromal signals due to cellular dysfunction
Stromal dysfunction to due previous hematologic malignancy
Adaptive immunity (climate)
Proinflammatory T-cell and innate response directed at key NHSC
HSC suppression by inflammatory cytokines such as IFN-γ
Impaired thymopoiesis and generation of T-regs

PRABAHRAN et al, Blood Advances. 2022 Mar 22;6(6):1947-59.

HSCs (seed)

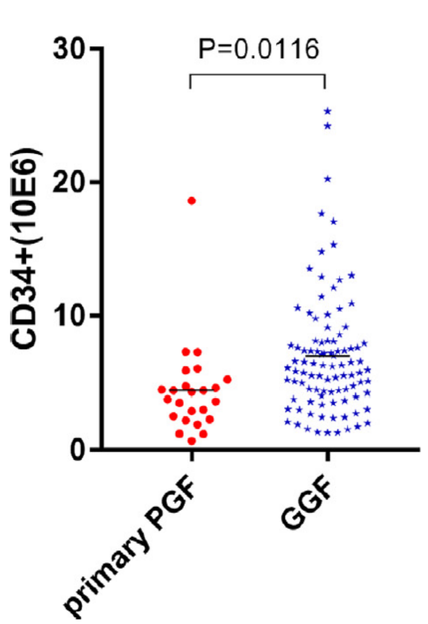
CD34+ cells ≥ 5 x 106/kg are currently recommended as the optimal dose by the EBMT.

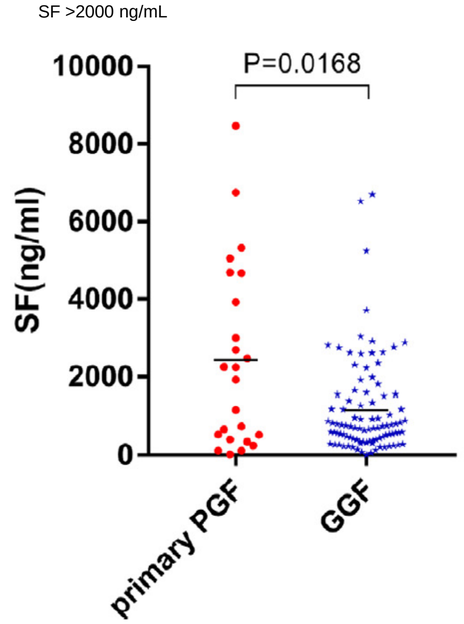
CD34 is also an established marker of other non-hematopoietic cells, including vascular endothelial progenitor cells (EPCs), mesenchymal stem cells (MSCs), and embryonic fibroblasts.

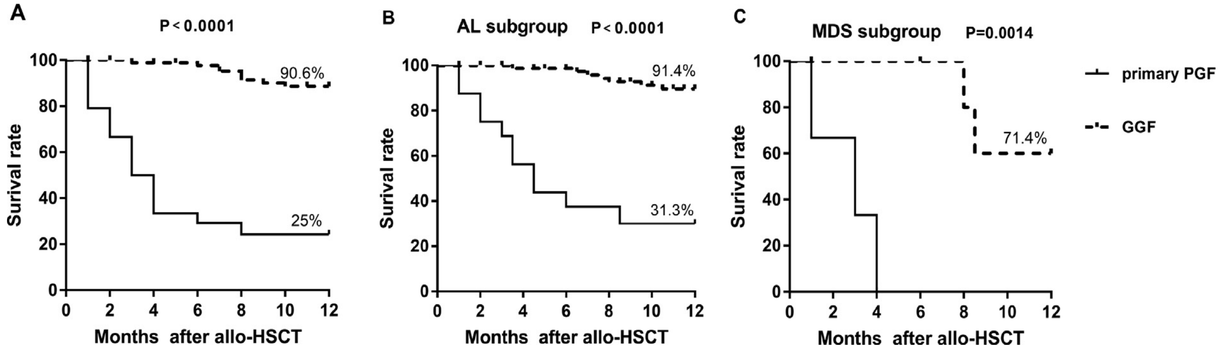
Collected "CD34+ cells" should not be confused with **"CD34+ HSPCs"**.
New HSPCs markers (including CD150, CD48, and CD244) may enrich the purer stem cell population.

Multivariate Logistic Analysis of Risk Factors for Primary PGF

Potential Risk Factors (P <.10)	All Allo-HSCT Recipients		AL and MDS Subgroup	
	P value	OR	P value	OR
Disease	.096			
Time from diagnosis to HSCT, mo	.279		.256	
Splenomegaly	**.039**	**3.306**	.111	
Disease state at HSCT	.324		.341	
Risk stratification	.226		.294	
Donor type	.763		.195	
SF level, ng/mL	**.008**	**4.417**	**.031**	**3.408**
$CD34^+$ cell dose, $\times 10^6$/kg	**.003**	**5.089**	**.003**	**5.635**
CMV infection in 30 d	.642		.657	







Y. Zhao et al. / Biol Blood Marrow Transplant 25 (2019) 18981907

Virus reactivation and low dose of CD34+ cell, rather than haploidentical transplantation, were associated with secondary poor graft function within the first 100 days after allogeneic stem cell transplantation

	Overall cohort			Haploidentical donor			Matched sibling donor		
	p	HR	95%CI	p	HR	95%CI	*p*	HR	95%CI
CD34 cell (< median)	0.019	3.070	1.207–7.813	0.049	2.803	1.006–7.810	0.565		
CMV reactivation	0.003	7.827	2.002–30.602	0.047	4.538	1.021–20.165	0.004	43.03	3.256–568.664
EBV reactivation	0.009	3.648	1.382–9.629	0.006	4.101	1.504–11.183	0.992		
Grades 2–4 aGVHD	0.215			0.121			0.386		
MDS versus other	0.143			0.179			0.317		
HID versus MSD	0.141			–			–		

- The median time of sPGF was 54.5 (34-91) days after transplantation.

- EBV reactivation and CMV reactivation were identified as independent risk factors for sPGF.

Annals of Hematology (2019) 98:1877–1883

HSCs (seed)

It is essential to maintain **high-quality stem cells** at each step of the transplantation process.

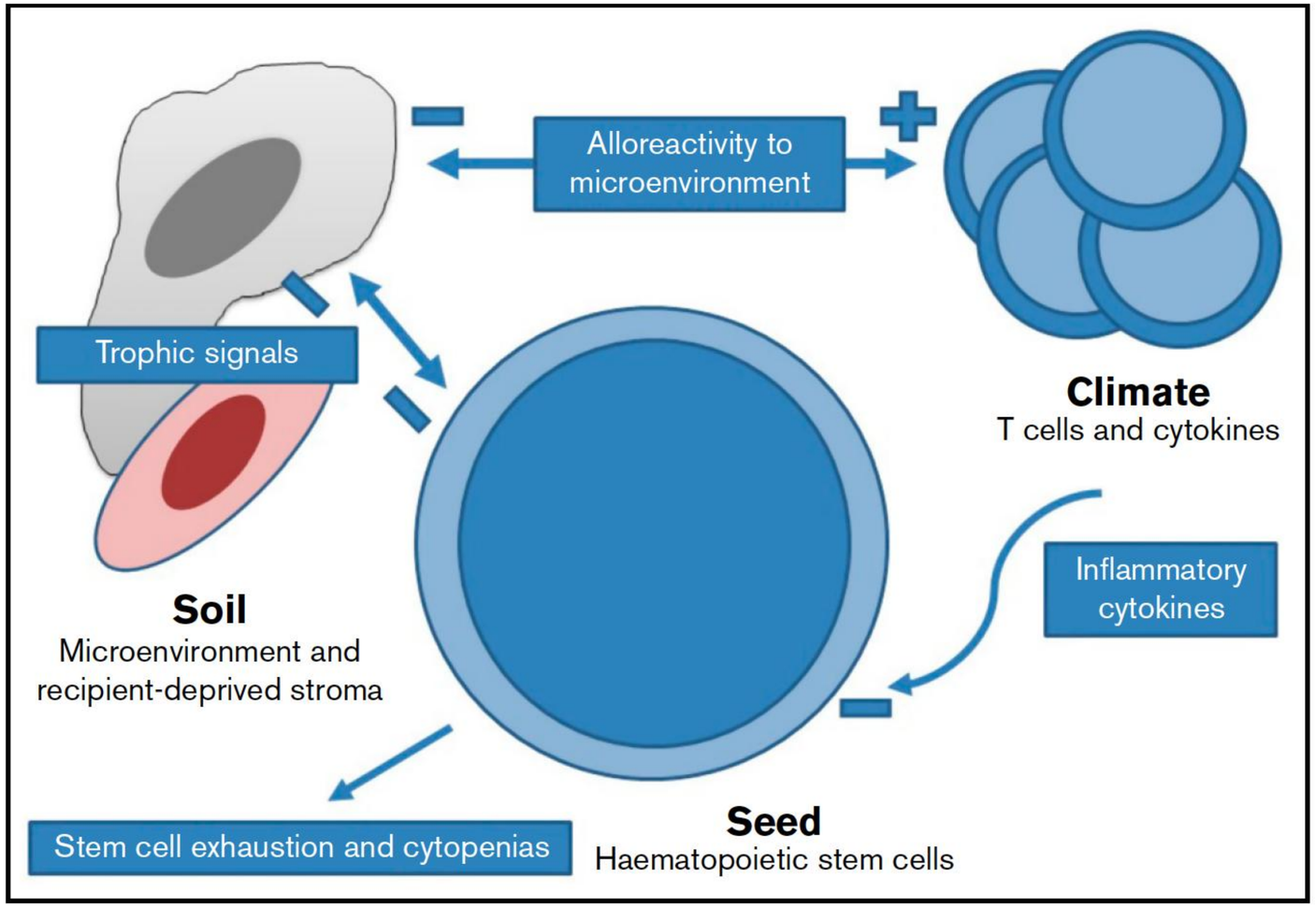
There are no studies evaluating whether PGF specifically occurs more frequently in frozen vs fresh donations.

Optimization of the cell handling, freezing, and thawing steps to ensure stem cell quality.

Although methods for improving the viability and recovery rate of thawed stem cells are continuously being developed, the procedures still have a negative effect on the product quality and potency.

Colony assays are the gold standard for stem cell proliferation and differentiation potency in vitro, which are used as an additional quality criterion.

Seed, soil, and climate model of Poor graft function (PGF)



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PRABAHRAN et al, Blood Advances. 2022 Mar 22;6(6):1947-59.

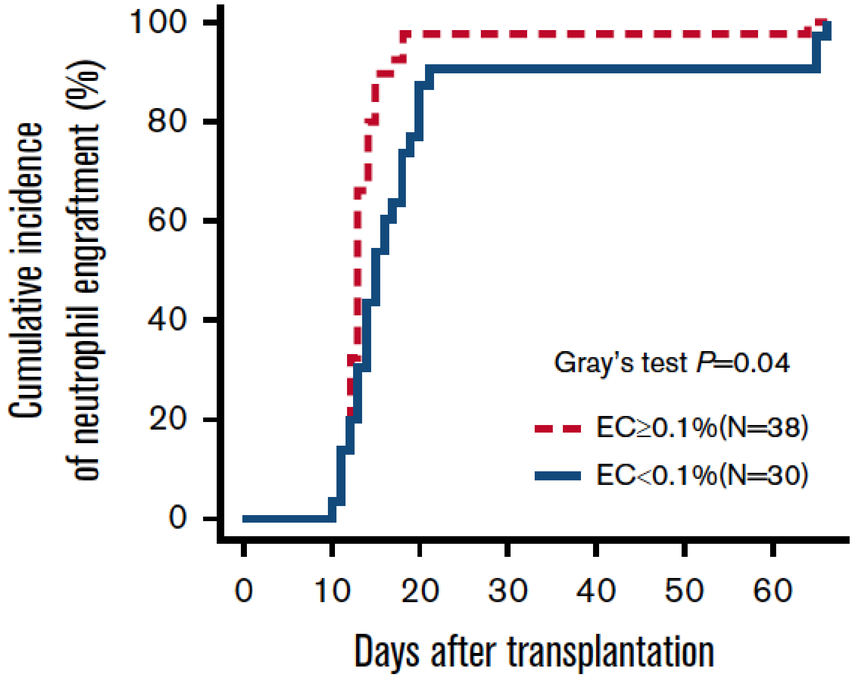
Bone marrow microenvironment (soil)

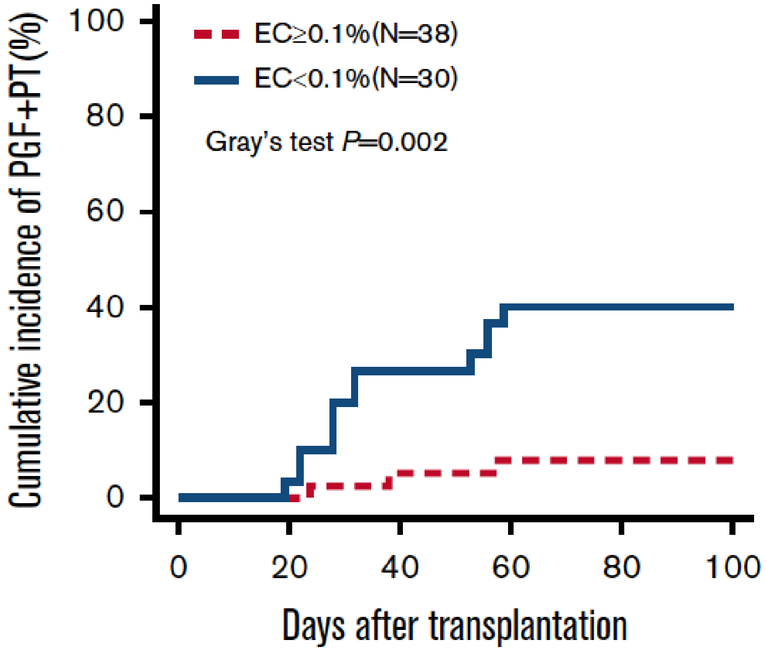
Endothelial Cells (ECs)
Mesenchymal Stem Cells (MSCs)

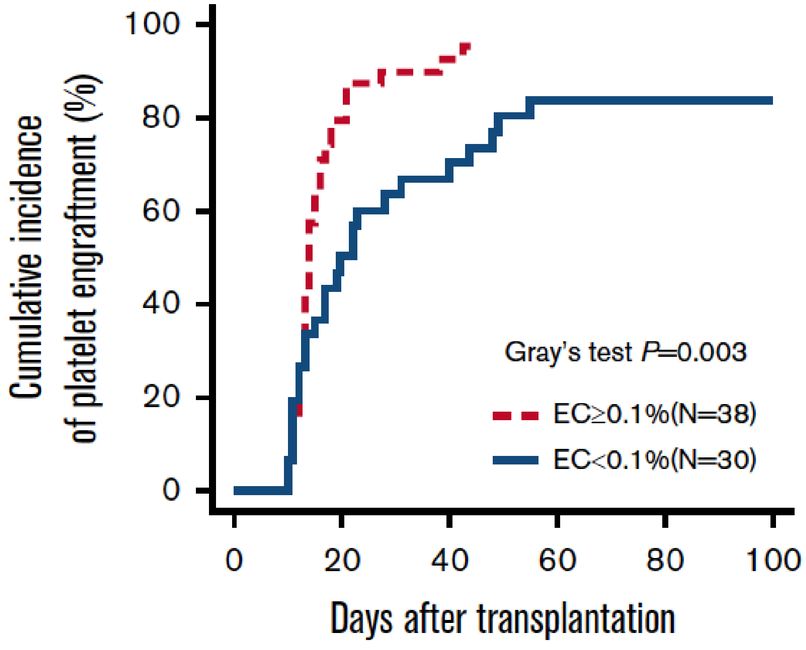
Both ECs and MSCs express molecules, such as CXCL12 and stem cell factor, needed for stem cell maintenance and engraftment post-alloSCT.

Dysfunction of MSCs and ECs, as nonhematologic stromal cells has been associated with PGF.

PGF and PT patients demonstrated defective BM ECs pre-HSCT and impaired dynamic reconstitution of BM ECs and CD34+ cells at early time points post-HSCT.



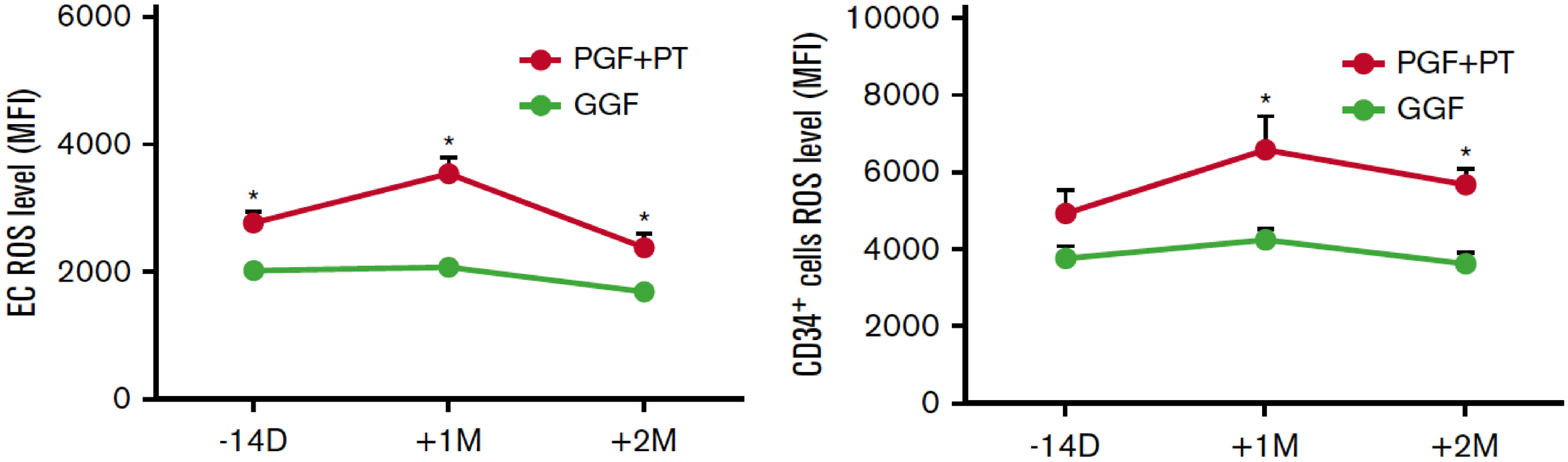




KONG et al. Blood Advances. 2019 Apr 23;3(8):1303-17.

Reactive oxygen species (ROS) induce exhaustion of CD34+ cells in PGF patients post-HSCT.

ROS play an important role in the control of EC function and vascular integrity.



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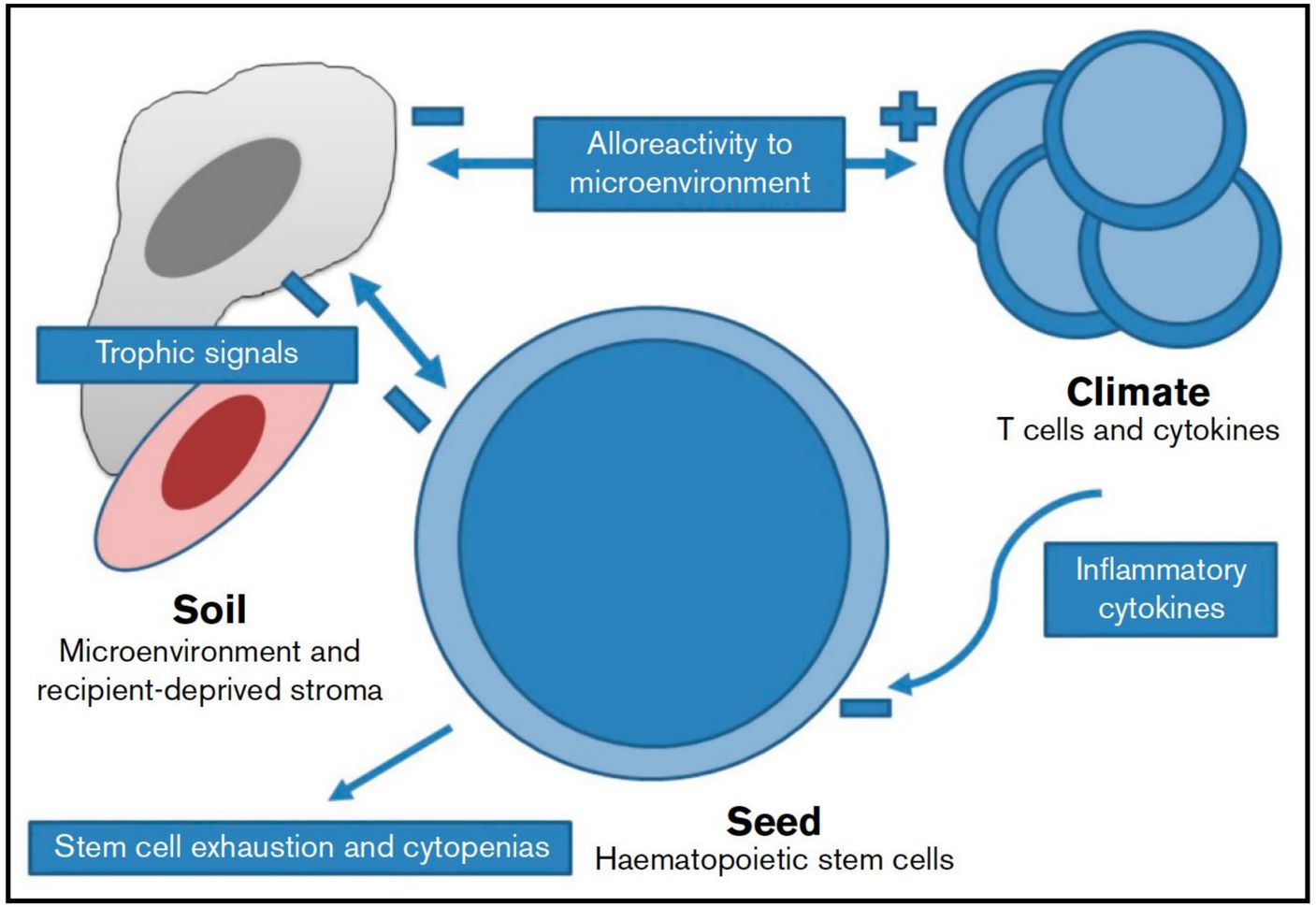
Seed, soil, and climate model of Poor graft function (PGF)



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PRABAHRAN et al, Blood Advances. 2022 Mar 22;6(6):1947-59.

Immune dysfunction (Climate/Insects)

Graft-versus-bone marrow response
Immune dysregulation (abnormal Th17/T-reg ratio)
Donor-Specific Anti-HLA Antibodies
Viral reactivation
Iron Overload

Management of PGF

- Stem cell–directed therapy
- Bone marrow microenvironment and stromal cell–directed therapy
- ROS
- Immune-directed therapy

Stem cell–directed therapy

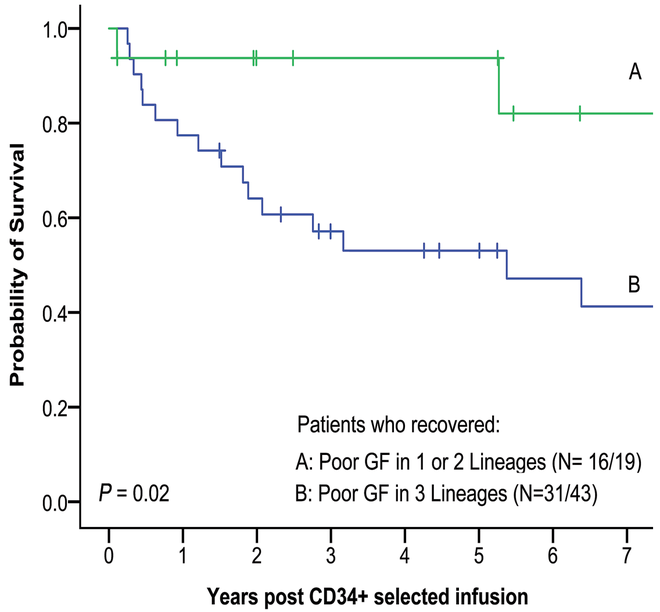
Re-establishment or augmentation of hematopoiesis using CD34 selected stem cell reinfusions by providing HSCs without an alloreactive T-cell component

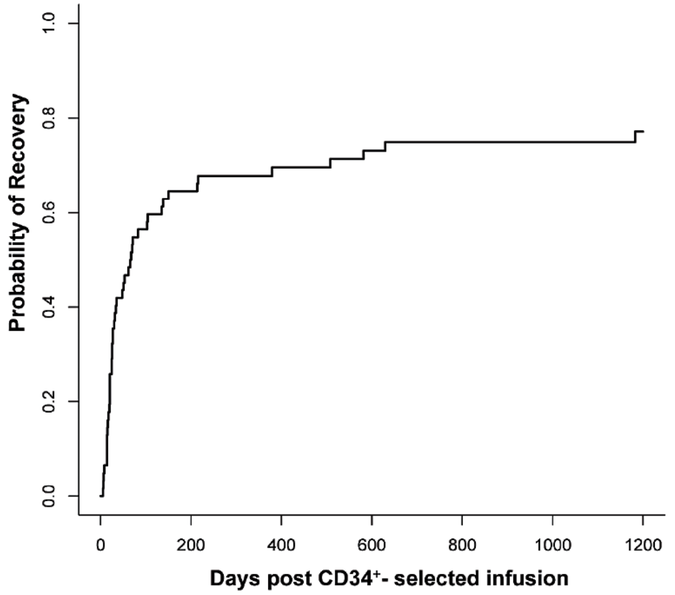
TPO (thrombopoietin) agonist

Predictors of recovery following allogeneic CD34+-selected cell infusion without conditioning to correct poor graft function

Multivariate analysis for recovery after CD34+- selected infusion

	N	OR (95% CI)	*P*-value
Active infection at the time of CD34⁺-selected infusion			
Yes	24	1.0	
No	36	38.9 (3.9-388.3)	0.002
Missing values	2		
R/D CMV status			
Other	37	1.0	
Negative/negative	23	16.8 (1.4-195.8)	0.02
Missing values	2		
R/D sex			
Unmatched	31	1.0	
Matched	29	24.4 (2.3-254.5)	0.008
Missing values	2		



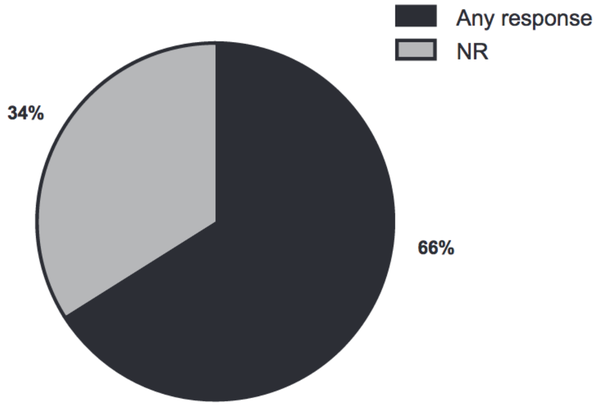


Fresh G-CSF–mobilized CD34-selected cells without conditioning

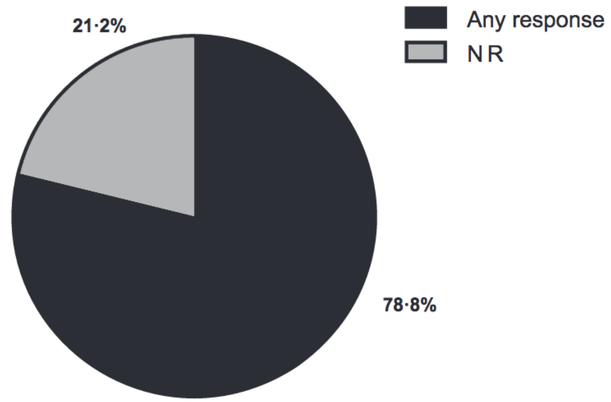
M.M. Cuadrado et al.Haematologica 2020, Volume 105(11):2639-2646

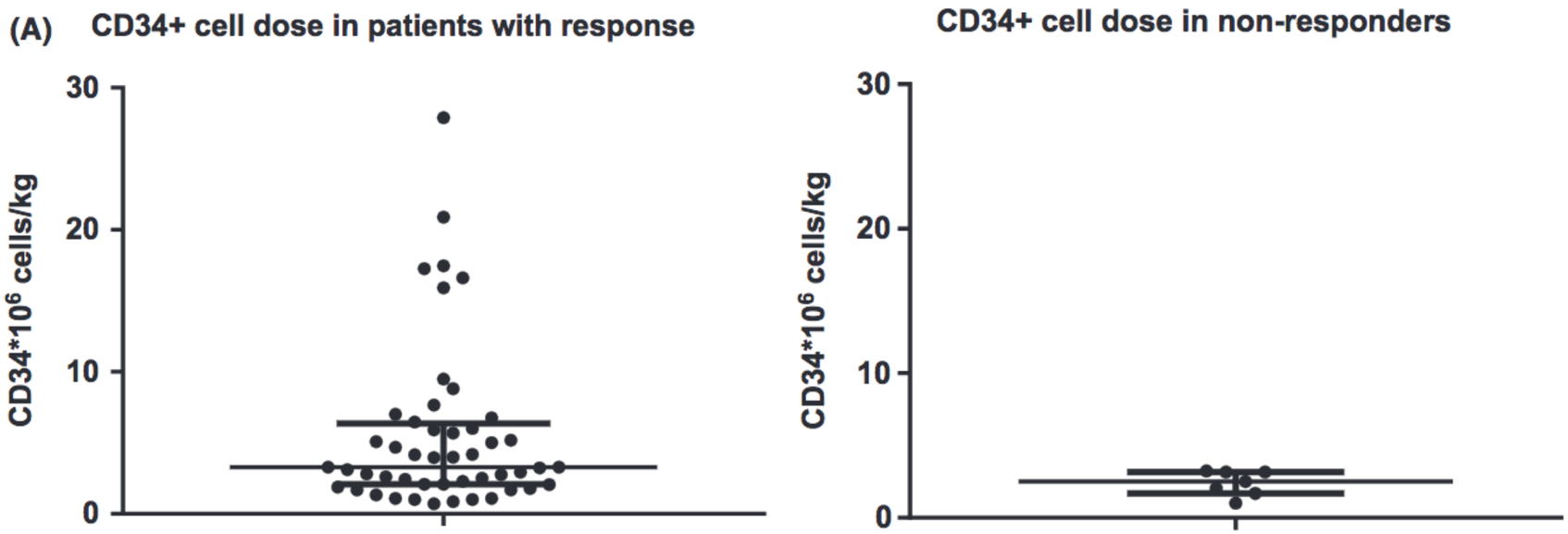
CD34+selected stem cell boosts can improve poor graftfunction after paediatric allogeneic stem cell transplantation

TP1; 4 weeks after stem cell boost



TP2; 8 weeks after stem cell boost





Comparison between infused CD34+ cell doses (2.078–6.353 9 106/kg) in patients who achieved a response and non-responding patients.

C. Mainardiet al. British Journal of Haematology, 2018,180,90–99

Fresh or Cryopreserved CD34+ Selected Mobilized PB Stem and Progenitor Cells for the Treatment of PGF after Allo-HSCT

CD34-selected product mobilized using the following strategies:

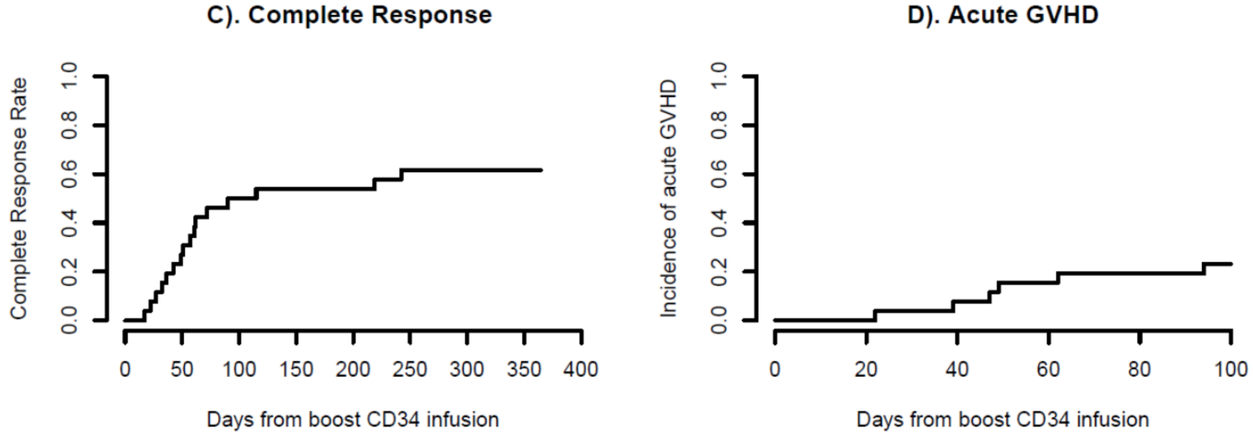
- fresh mobilized products using G-CSF and plerixafor (9); CR rate: 63%
- fresh mobilized products, using G-CSF only (9)
- cryopreserved cells mobilized by using G-CSF (8); CR rate: 63%
- All without conditioning

Number of CD34+ cells was higher in the freshly mobilized products compared to cryopreserved products (p<0.001).

Median CD34+ cells/kg (106) Post-Selection: **3.2**

Median CD3% Post-Selection: 0.2%

Complete Response : 62%



Biology of Blood and Marrow Transplantation. 2017 Jul 1;23(7):1072-7.

Comparisons of recent clinical research in the treatment for PGF

	Treatment	Dose	No. of patients	Response rate	Long-term survival rate	Adverse events/ incidence rate
Stasia *et al.*[67]	$CD34^+$-selected SCB	3.4×10^6/kg (median)	41	83%	3-year survival: 63%	aGVHD (15%)
Haen *et al.*[68]	$CD34^+$-selected SCB	4.6×10^6/kg (median)	20	90% in platelets 95% in leukocytes 90% in hemoglobin	2-year survival: 53%	aGVHD (5%)
Ghobadi *et al.*[69]	$CD34^+$-selected SCB	3.1×10^6/kg (G-CSF only) 10.9×10^6/kg (G-CSF plus plerixafor) 1×10^6/kg (cryopreserved products)	26	81%	1-year survival: 65%	aGVHD (23%) cGVHD (31%)
Mainardi *et al.*[70]	$CD34^+$-selected SCB	3.15×10^6/kg (median)	50	78.8%	5-year survival: 38.67%	aGVHD (6%)
Cuadrado *et al.*[71]	$CD34^+$-selected SCB	3.2×10^6/kg (median)	62	75.8%	5-year survival: 54%	aGVHD (11%) cGVHD (8%)

J Chen, H Wang et al. Ther Adv Hematol 2020, Vol. 11: 1–13

Can Planned CD34+ Stem Cell Boost Prevent Poor Graft Function after Peripheral Blood Haploidentical Hematopoietic Transplantation?

Objectives: planned CD34+ stem cell boost (SCB) after PTCy could be used to prevent PGF after haplo-HCST.

Part of the donor product underwent CD34+ selection and cells were cryopreserved.

On day 5-6, CD34+ selected donor product was infused.

All nine SCB patients had neutrophil engraftment (NE) with a median time of 16 days (13 25) compared with 17 days (12 78) in the comparison cohort **(p = 0.40)**.

Six of eight evaluable SCB patients had platelet engraftment (PE) with a median time of 22.5 days (12 55) compared with 26 days (9 134) in the comparison cohort **(p = 0.675)**.

Leukemia & Lymphoma. 2021 Feb 23;62(3):749-51.

TPO (thrombopoietin) agonism

c-MPL is expressed on HSCs.

Eltrombopag may also improve stem cell renewal and increase the amount of functional stem cells due to reduction in intracellular iron by eltrombopag-mediated iron chelation.

Successful treatment of secondary poor graft function post allogeneic hematopoietic stem cell transplantation with eltrombopag

12 patients; poor response to standard treatments for sPGF after allo-HSCT.

Eltrombopag: 25 mg/d for 3 days and then increased to 50 or 75 mg/d.

Median treatment duration: **8 (2–23) weeks**.

Ten patients (**83.3%**) responded to the treatment.

The time from eltrombopag initiation to achieving CR was **29 (10–49) days**.

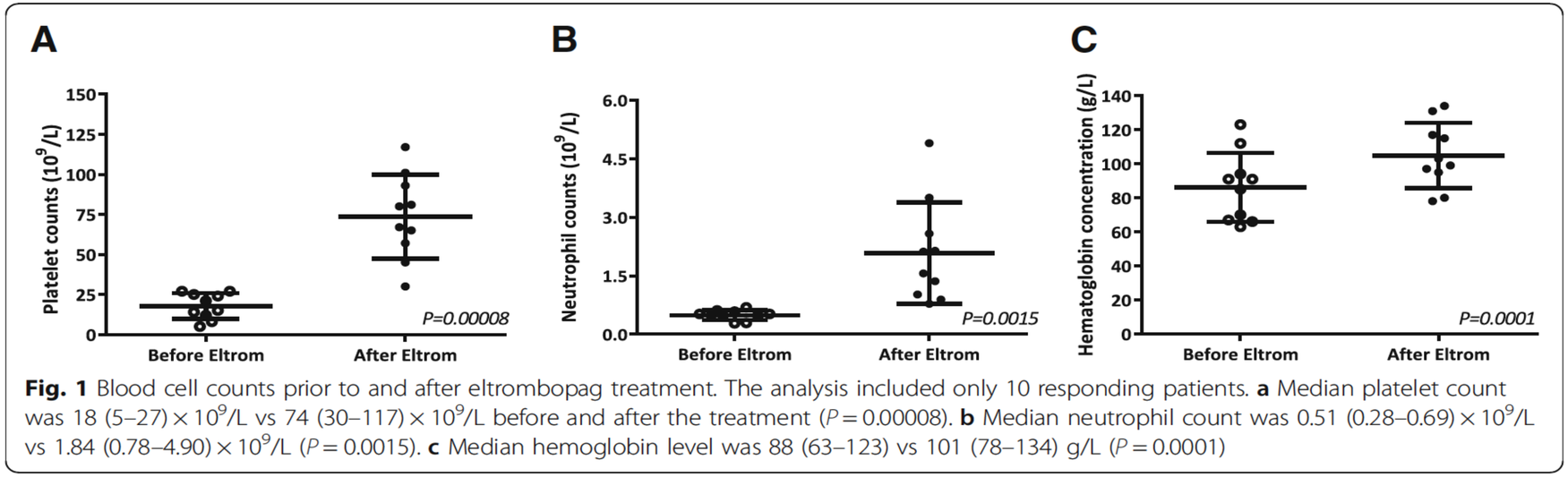


Fig. 1 Blood cell counts prior to and after eltrombopag treatment. The analysis included only 10 responding patients. **a** Median platelet count was 18 (5–27) × 10^9/L vs 74 (30–117) × 10^9/L before and after the treatment ($P = 0.00008$). **b** Median neutrophil count was 0.51 (0.28–0.69) × 10^9/L vs 1.84 (0.78–4.90) × 10^9/L ($P = 0.0015$). **c** Median hemoglobin level was 88 (63–123) vs 101 (78–134) g/L ($P = 0.0001$)

Tang et al. Journal of Hematology & Oncology (2018) 11:103

Eltrombopag for the treatment of poor graft function following allogeneic stem cell transplant: a retrospective multicenter study

International Journal of Hematology. 2021 Aug;114(2):228-34.

	All patients ($N=48$)		Tri-lineage ($n=20$)	
	Response, %	p value	Response, %	p value
Age: <60 vs ≥ 60 years	75 vs 72	0.8	85 vs 57	0.1
Recipient: male vs female	81 vs 69	0.3	78 vs 73	0.7
Diagnosis: PMF vs other	89 vs 71	0.2	100 vs 69	0.1
Disease phase: CR vs no CR	88 vs 71	0.2	89 vs 63	0.1
Donor type				
MRD vs MUD vs HAPLO	100 vs 87 vs 54	**0.02**	100 vs 88 vs 43	**0.04**
Matched vs HAPLO	92 vs 52	**0.002**	94 vs 38	**0.0009**
Stem cell source: BM vs PB	62 vs 81	0.1	50 vs 84	0.1
CD34: $<$ vs $\geq 4\times10^6$/kg	71 vs 72	0.6	50 vs 92	**0.03**
ABO: major mismatch vs minor mismatch vs match	82 vs 80 vs 67	0.5	80 vs 100 vs 66	0.7
Transplant-EPAG interval $<$ vs ≥ 90 days	61 vs 88	**0.03**	53 vs 86	**0.04**
Platelets: $<$ vs $\geq 10\times10^9$/L	70 vs 80	0.6		
Cytopenia: primary vs secondary	73 vs 80	0.3	68 vs 80	0.5

Comparisons of recent clinical research in the treatment for PGF

	Treatment	Dose	No. of patients	Response rate	Long-term survival rate	Adverse events/ incidence rate
Tang *et al.*[74]	Eltrombopag	Initiated at 25 mg/day for 3 days and then increased to 50 or 75 mg/d	12	83.3%	1-year survival: 83.3%	No severe adverse event
Fu *et al.*[75]	Eltrombopag	initiated at 25 or 50 mg/day and adjusted to a maximum of 50–100 mg/day	15	60.0%		No severe adverse effect
Marotta *et al.*[76]	Eltrombopag	initiated at 50 mg/day, and adjusted to 150 mg	12	58.3%		Skin hyperpigmentation (8.3%)

J Chen, H Wang et al. Ther Adv Hematol 2020, Vol. 11: 1–13

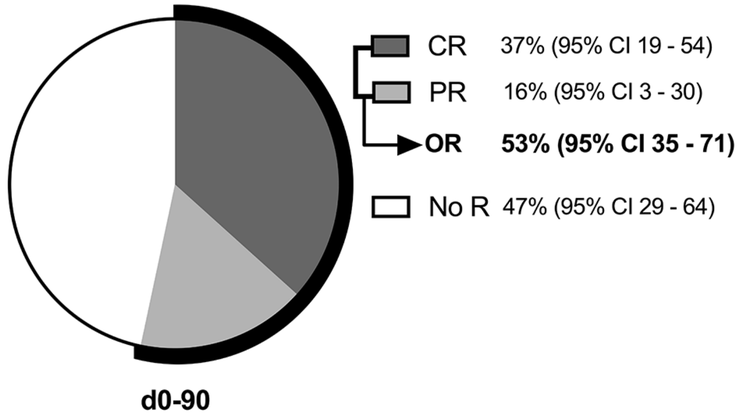
Bone marrow microenvironment and stromal cell– directed therapy

- Mesenchymal stromal cells
- N-acetyl-L-cysteine

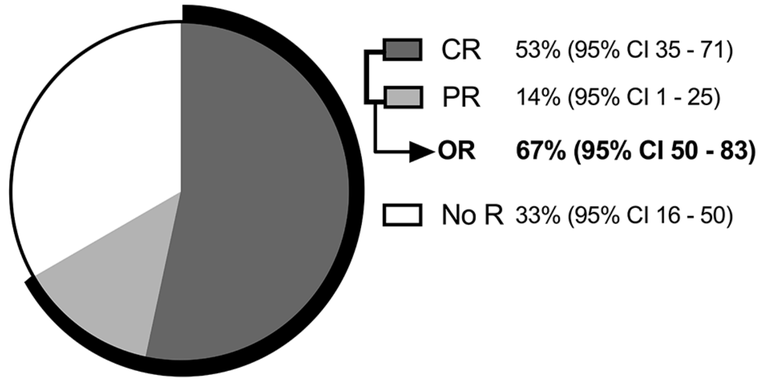
Multipotent mesenchymal stromal cells as treatment for PGF after allogeneic HSCT: A multicenter prospective analysis

Servais et al. Frontiers in Immunology.;14:273.

30 patients with prolonged severe cytopenia and PGF after allo-HSCT
MSC (Third party): a single i.v. infusion at a dose of 1-2 million(s) cells/kg

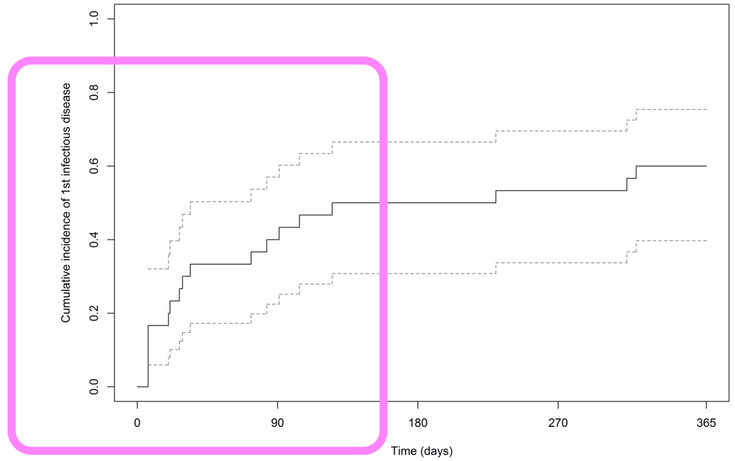


d0-90



d0-180

Poor graft function after alloHCT		
3/2/1 cytopenia, n (%)	3/17/10	(10)/(57)/(33)
Anemia, n (%) Thrombocytopenia, n (%) Neutropenia, n (%)	26 22 5	(87) (73) (17)
Primary poor graft function, n (%) Secondary poor graft function, n (%)	22 8	(73) (27)
Prior donor CD34^{+} stem cell boost, n (%)	4	(13)
Delay from alloHCT to MSC infusion, median (range), days	159	(42-595)



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Liu *et al.*[72]	MSC	1×10^6/kg (1–3 times)	20	85%	508 days: 45% (median follow-up time)	Infection (65%) CMV DNA viremia (10%) EBV DNA viremia (35%) EBV-associated PTLD (15%) GVHD (15%)
Servais *et al.*[73]	MSC	$1\text{-}2\times10^6$ /kg (single time)	30	51.8% (day90) 69.2% (day180)	1-year survival: 70%	No severe adverse event

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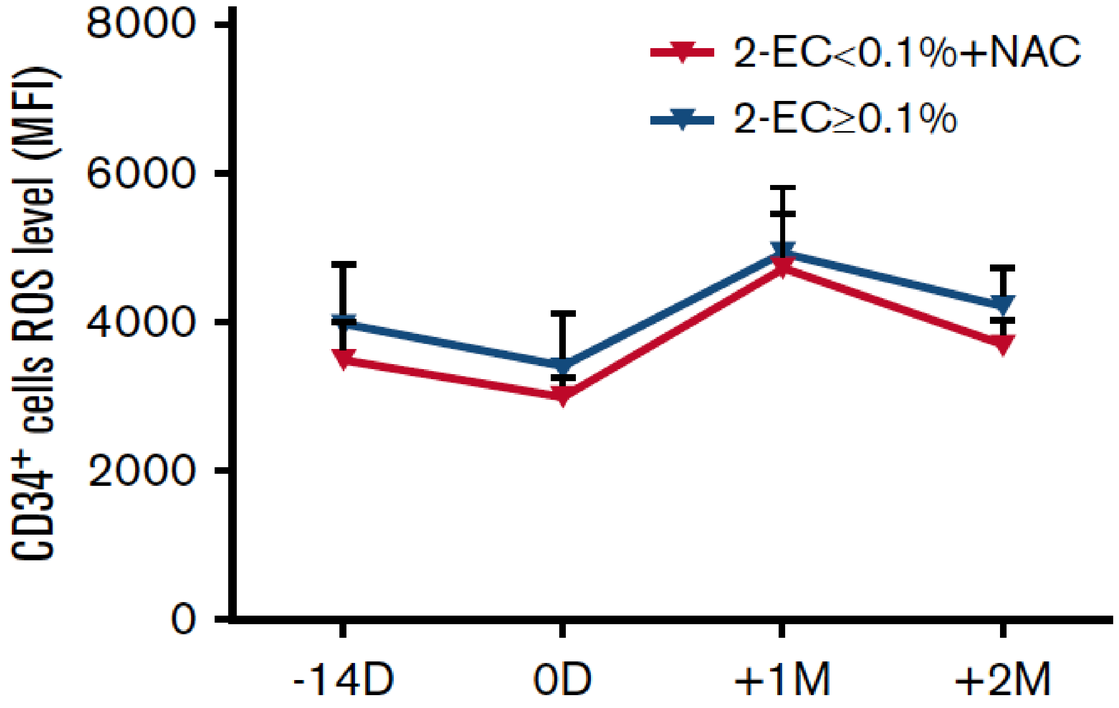
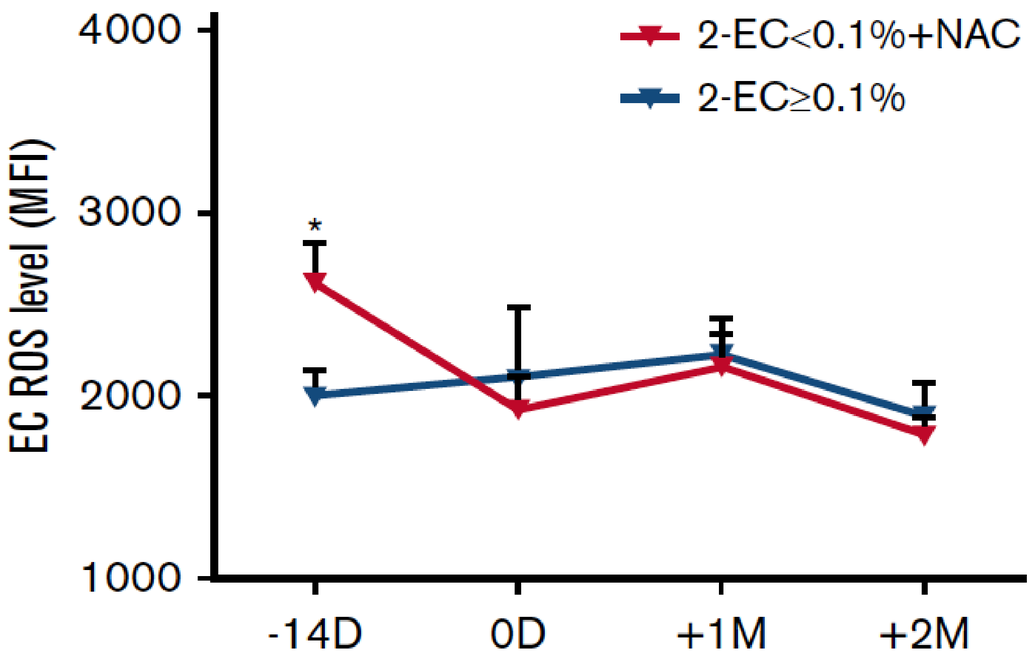
Prophylactic oral NAC reduced poor hematopoietic reconstitution by improving endothelial cells after haploidentical transplantation





KONG et al. Blood Advances. 2019 Apr 23;3(8):1303-17.

Management of PGF

Seed, soil, or climate: which therapy is best?

PGF due to preexisting bone marrow microenvironment dysfunction:

- Preexisting myeloproliferative or longstanding myeloid malignancies.
- Marrow fibrosis and/or inflammatory bone marrow microenvironment with or without splenomegaly.
- Post-alloSCT treatments for this type of PGFare limited.
- **TPO agonism** may be useful.

PGF due to significant intratransplant illness

- Patients who have multiorgan dysfunction in the setting of profound sepsis or veno-occlusive disease within the first 30 days of alloSCT.
- HSC-stimulating therapies such as repeat **HSC infusion** or TPO agonism may be considered.

PGF due to posttransplant inflammatory stimuli

- Occurs due to consequences of viral infection plus or minus treatment of viral infection or GVHD.
- Treatment of the underlying cause
- **TPO agonism** may be useful

Thank you

Mixed Donor Chimerism (MC) in Allo-HSCT

5% to 95% for both myeloid and lymphoid lineages.

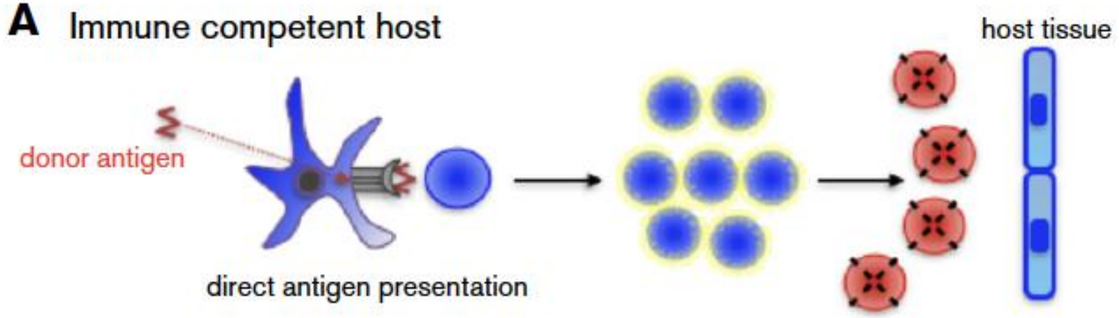
Mixed Chimerism, the coexistence of donor and recipient hematopoiesis after allo-HSCT, increases the risks of GF and recurrence of the original disease.

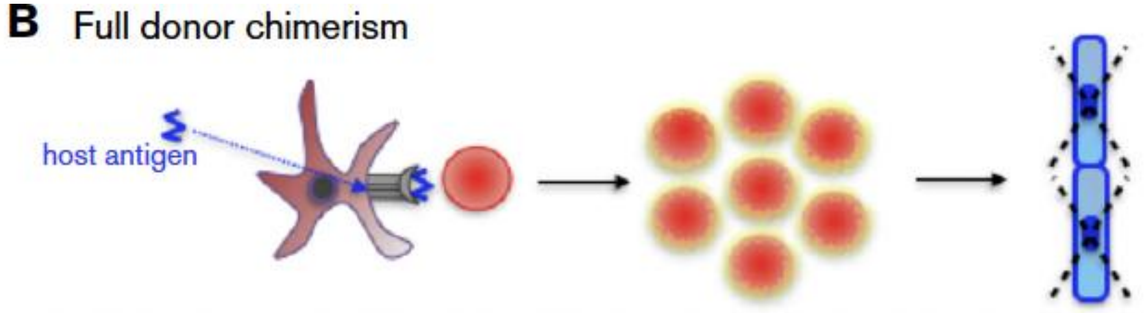
A dynamic state in which a progressive decline in donor chimerism might portend or confirm graft loss or disease recurrence.

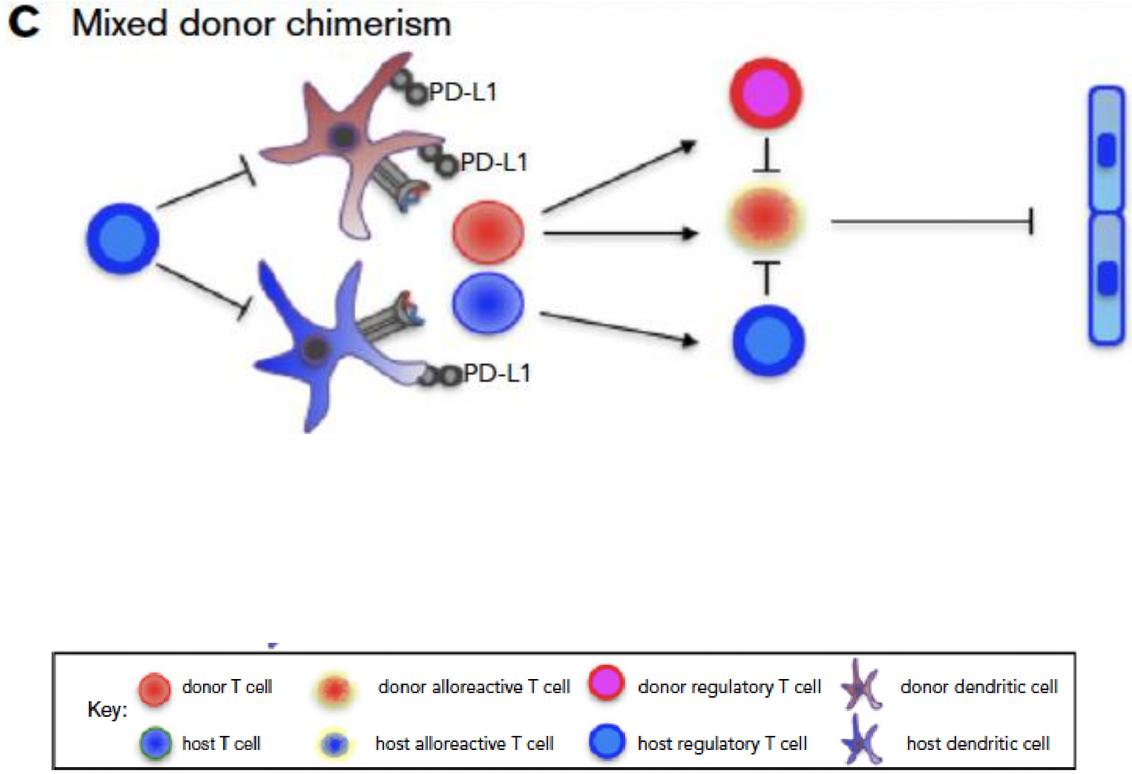
Lower levels of mixed donor chimerism are likely to be treated differently than those with higher levels.

- Non-malignant diseases
- Malignant diseases
- Non-myeloablative stem cell transplants
- Myeloablative stem cell transplants
- Graft type

Mixed chimerism in SCT: conflict or peaceful coexistence?







Managing Mixed Donor Chimerism (MC)

- **Malignant diseases**

Consider using the actual percentages of donor myeloid cells and lymphoid cells, blood counts and the clinical status of the patient for a change in management.

- **Nonmalignant diseases/bone marrow failure syndromes**

Level of donor chimerism required for disease correction depends on the disease.

Classification of non-maligant disorders with associated lineage specific engraftment, and recommended donor chimerism levels for adequate disease mitigation.

Non-malignant disorder	Lineage specificity	Minimum goal for donor Chimerism
Immunodeficiencies		
HLH	NK cell/Lymphoid	>30% (13)
IPEX, ALPS	Lymphoid	>50% (32)
Severe Combined Immunodeficiency	T, B, NK cell	100% (8)
Chronic Granulomatous Disease	Myeloid	>50% (5)
Wiskott-Aldrich Syndrome	Lymphoid/Myeloid	>50% (16)

Non-malignant disorder	Lineage specificity	Minimum goal for donor Chimerism
Hemoglobinopathies		
Sickle Cell Disease	Erythroid/myeloid	20–25% (23)
Thalassemias	Erythroid/myeloid	20–25% (27)
Metabolic disorders		
ALD, Hurlers, Krabbe's	Myeloid	70–100% (1)
Osteopetrosis	Myeloid	>10% (20)
Bone marrow failure syndromes		
SCN, SDS, DBA, FA	Myeloid	100% (30)
	Lymphoid	>50% (31)

Zimmerman and Shenoy, August 2020 | Volume 11 | Article 1791

Transplantation physician responses to options for managing down-trending chimerism in malignant diseases.

A

Options for down-trending CD3 donor chimerism	Pediatric-Transplant Panel member number															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Withdraw immune suppression	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■
Increase immune suppression															■	■
Donor Lymphocyte infusion			■				■		■	■	■	■	■	■	■	■
CD34 cell boost								■					■	■	■	
Second allogeneic HCT													■	■		■

B

Adult-Transplant Panel member number																			
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
										■		■	■					
					■		■	■	■	■	■	■	■	■			■	■
						■				■				■				■
										■			■	■				

C

Options for down-trending CD33 donor chimerism	Pediatric-Transplant Panel member number															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Withdraw immune suppression	■	■	■	■	■	■			■	■	■	■	■	■	■	■
Increase immune suppression							■	■								
Donor Lymphocyte infusion				■					■	■	■	■		■		■
CD34 cell boost		■					■			■				■	■	
Second allogeneic HCT				■										■	■	■

D

Adult-Transplant Panel member number																			
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
										■		■						
	■							■	■	■	■		■	■			■	■
							■	■	■	■	■	■	■	■		■		■
										■		■	■	■				

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Transplantation physician responses to options for managing down-trending chimerism in non-malignant diseases.

A

Options for down-trending CD3 donor chimerism	Pediatric-Transplant Panel member number																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Withdraw immune suppression	■	■		■	■	■	■	■			■	■	■	■	■	■	
Increase immune suppression					■	■		■	■	■	■	■			■	■	■
Donor Lymphocyte infusion			■			■	■				■	■			■	■	
CD34 cell boost					■			■					■	■			
Second allogeneic HCT				■		■							■	■	■	■	

B

Adult-Transplant Panel member number															
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
■	■	■	■	■	■		■	■	■	■	■	■		
						■				■		■	■	■
							■	■	■		■	■	■	■
						■				■				■
													■	■

C

Options for down-trending CD33 donor chimerism	Pediatric-Transplant Panel member number																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Withdraw immune suppression	■	■	■	■	■	■		■			■	■	■	■	■	■	
Increase immune suppression					■	■			■	■	■	■			■	■	■
Donor Lymphocyte infusion			■			■					■	■				■	
CD34 cell boost		■			■					■			■	■	■		
Second allogeneic HCT				■		■			■				■	■	■	■	

D

Adult-Transplant Panel member number															
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
		■	■	■	■	■	■	■	■	■	■	■		
										■		■	■	■
	■							■	■		■		■	■
■						■	■	■	■	■	■	■	■	■
											■	■	■	■

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Lineage-specific chimerism analysis

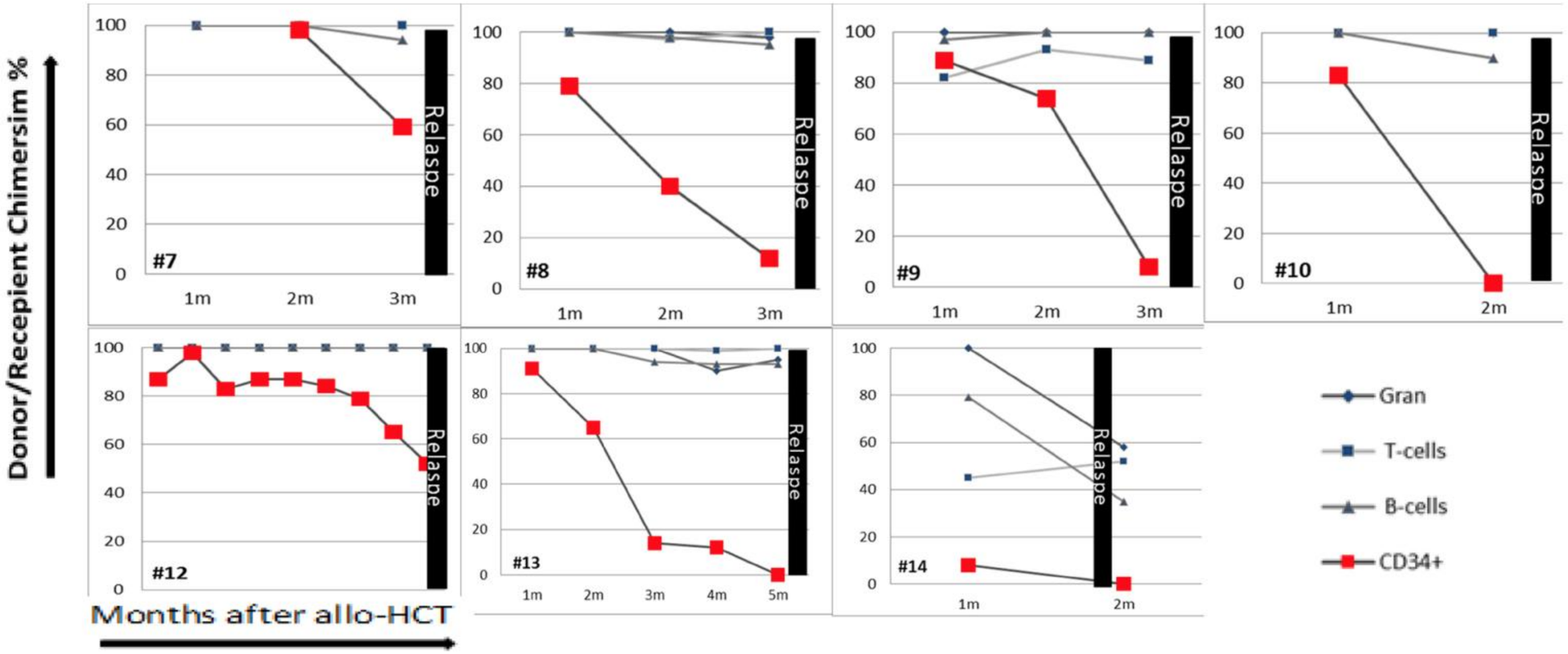
CD34+ chimerism

CD34+ donor chimerism of <80% had a 100% sensitivity for prediction of relapse.

Based on the available evidence, a decline in CD34+ donor chimerism occurs earlier prior to relapse compared to a decline in peripheral whole blood chimerism.

CD34 is expressed on the majority of blast cells in AML, MDS and ALL populations and can be used in in these patient populations as a more sensitive predictor of disease relapse compared to whole blood chimerism, especially in the absence of a disease-specific MRD marker.

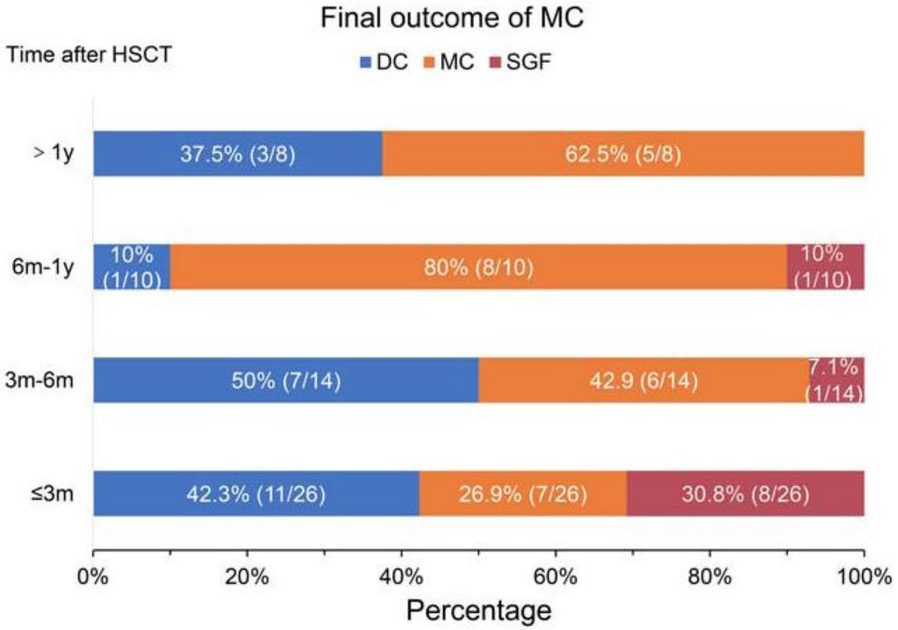
CD34+ chimerism analysis for minimal residual disease monitoring after allogeneic hematopoietic cell transplantation

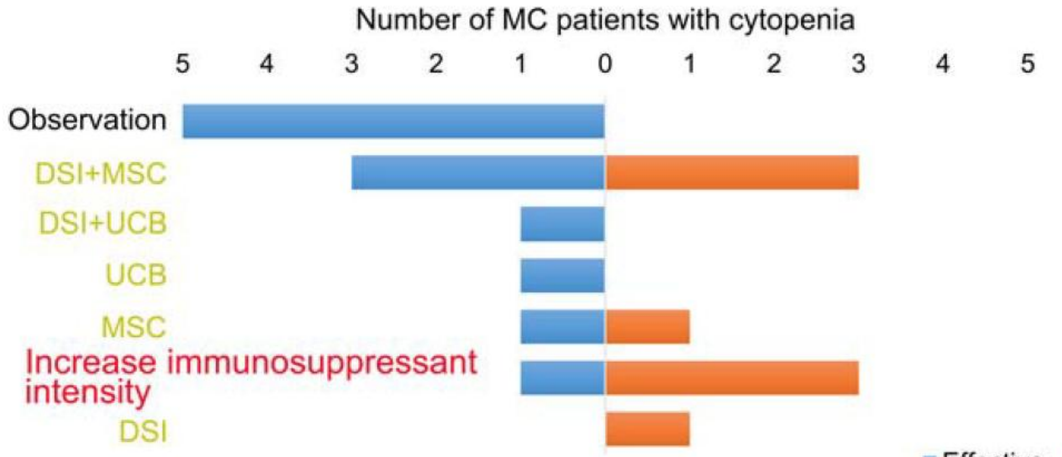


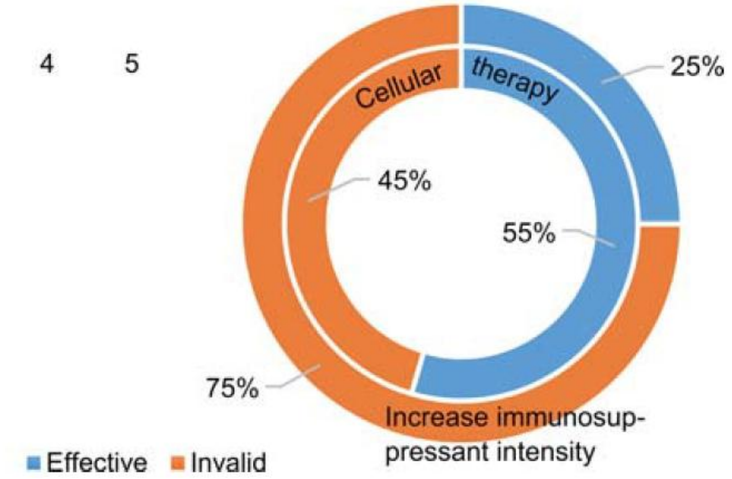
Decline of CD34+ donor chimerism could be documented at a median of 69 days prior to documentation of relapse (with a range of 4–175 days).

Leukemia Research 74 (2018) 110–112.

Mixed chimerism after allogeneic hematopoietic stem cell transplantation for severe aplastic anemia (SAA)

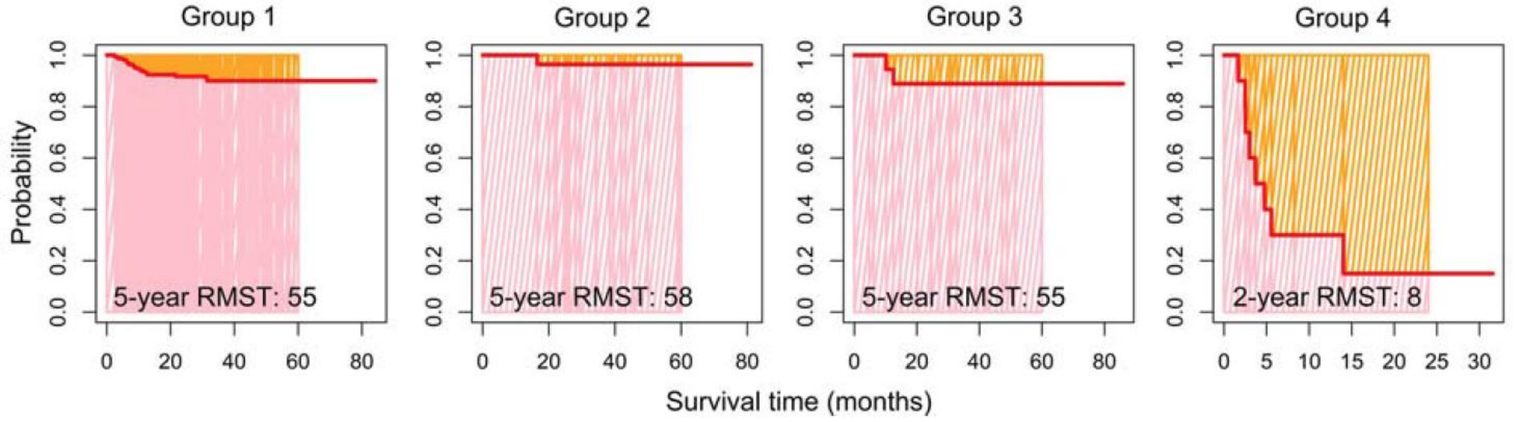






Y. ZHANG ET AL. HEMATOLOGY 2021, VOL. 26, NO. 1, 435–443

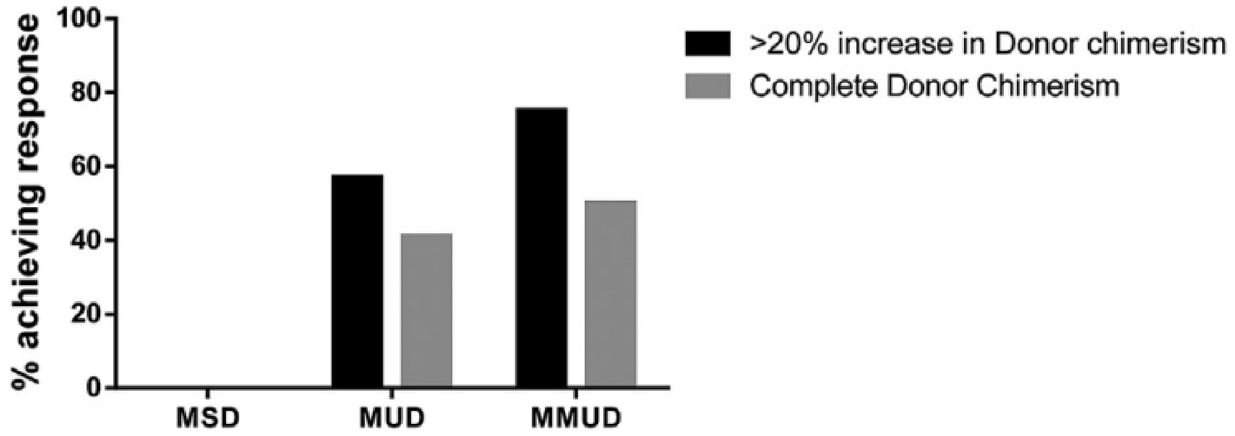
Group 1, donor chimerism (DC); group 2, mixed chimerism (MC) without cytopenia; group 3, MC with cytopenia; group 4, secondary graft failure (SGF).



Outcomes of Donor Lymphocyte Infusion for Treatment of Mixed Donor Chimerism after a Reduced-Intensity Preparative Regimen for Pediatric Patients with Nonmalignant Diseases

Transplant Characteristics of Patients Undergoing DLI for Mixed Donor Chimerism

Characteristic	All Patients
Diagnosis	
Hemophagocytic lymphohistiocytosis	16
Severe combined immunodeficiency	3
Omenn's syndrome	1
X-linked lymphoproliferative disease	3
Common variable immunodeficiency	1
Hurler's syndrome	1
Langerhans cell histiocytosis	1
IPEX	1
Sex	
Male	20
Female	7
Donor source	
Matched sibling bone marrow	4
8/8 unrelated donor	14
7/8 unrelated donor	8
6/8 unrelated donor	1
Median age at transplant, yr (range)	1.2 (.31-17)
Preparative regimen	
Proximal alemtuzumab	21
Distal alemtuzumab	6



H.L. Haines et al. / Biol Blood Marrow Transplant xxx (2014) 1-5

Graft failure (GF)

A significant cause of morbidity and mortality after allogeneic HSCT.

Estimated to occur in **1-5%** of cases after MAC and in up to **30%** of cases after RIC.

Primary graft failure:

No evidence of engraftment or hematological recovery of donor cells without evidence of relapse.

Secondary graft failure:

Loss of a previously functioning graft, resulting in cytopenia involving at least two blood cell lineages.

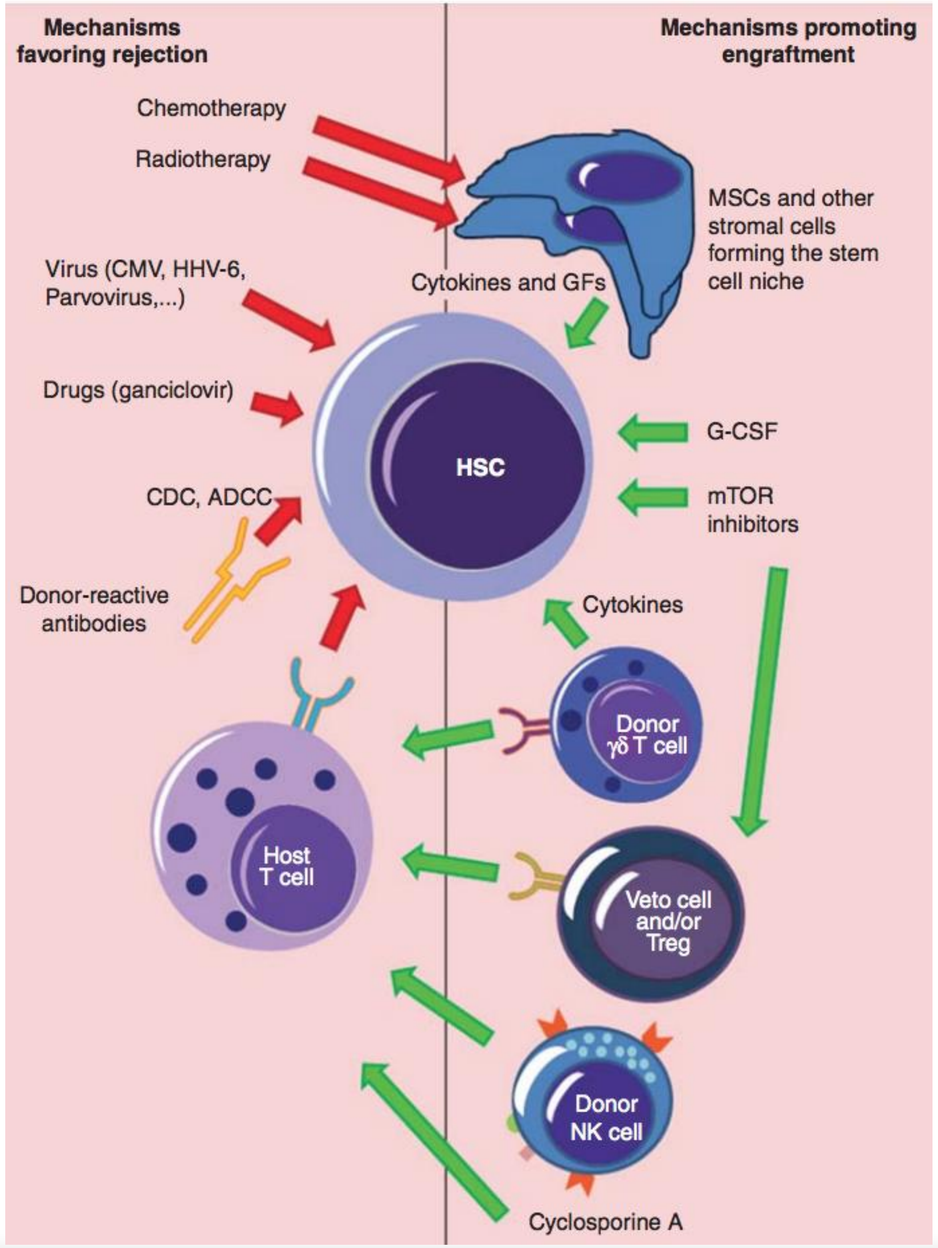
Primary graft failure is usually associated with a more relevant risk of morbidity and mortality in comparison with secondary graft failure

Graft failure (GF)

Several variables/risk factors, including:

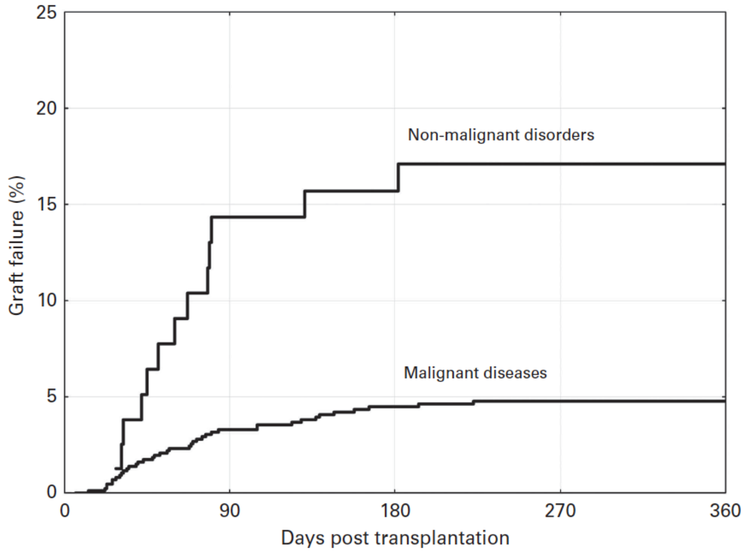
- HLA disparity & sex mismatch in the donor/recipient pair
- Presence of donor-specific antibodies (DSA) in the recipient
- Underlying disease
- Viral infections
- Type of conditioning regimen
- Source of stem cells
- T-cell depletion (TCD) of the graft
- Myelotoxic drugs in the post-transplant period

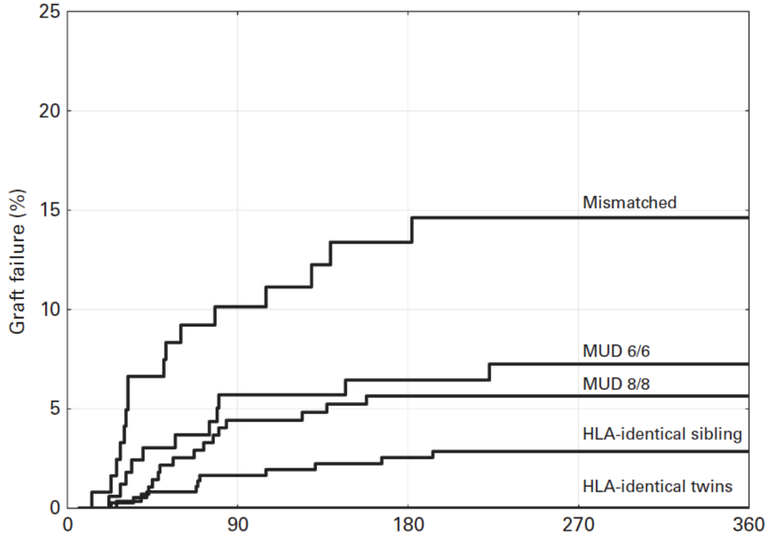
Differentiating graft rejection (as an immune-mediated process) from graft failure.

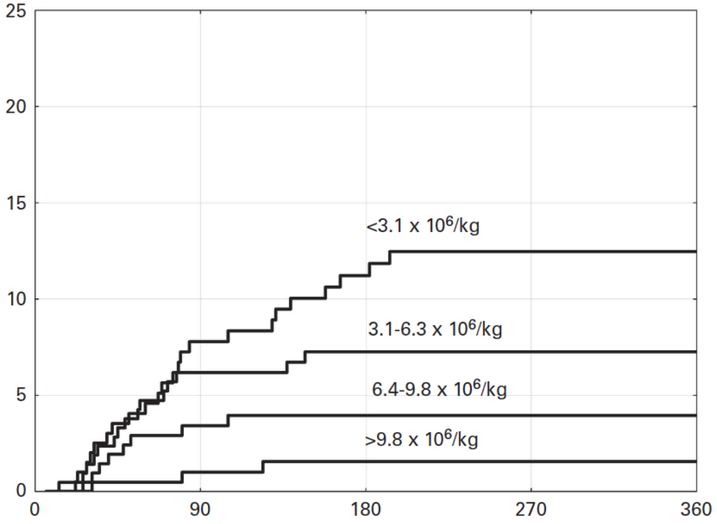


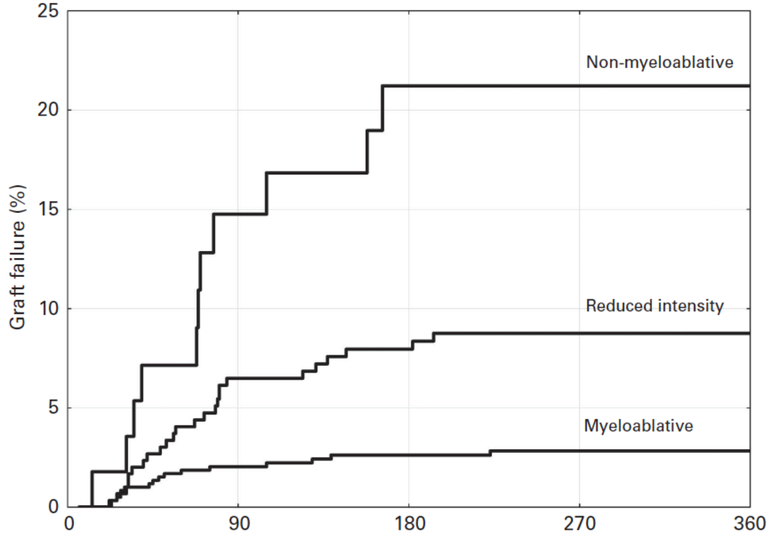
F. Locatelli et al.. Expert Opin. Pharmacother. (2014) 15(1):23-36

Graft failure in the modern era of allogeneic hematopoietic SCT









R Olsson et al. Bone Marrow Transplantation (2013) 48, 537–543