

Engrafman yetmezliđi

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ENGRAFMAN

-Nötrofil $>0.5 \times 10^9/L$,ardışık 3 günün ilk günü

-Trombosit $>20 \times 10^9/L$,ardışık 7 günün ilk günü

ENGRAFMAN YETMEZLİĞİ

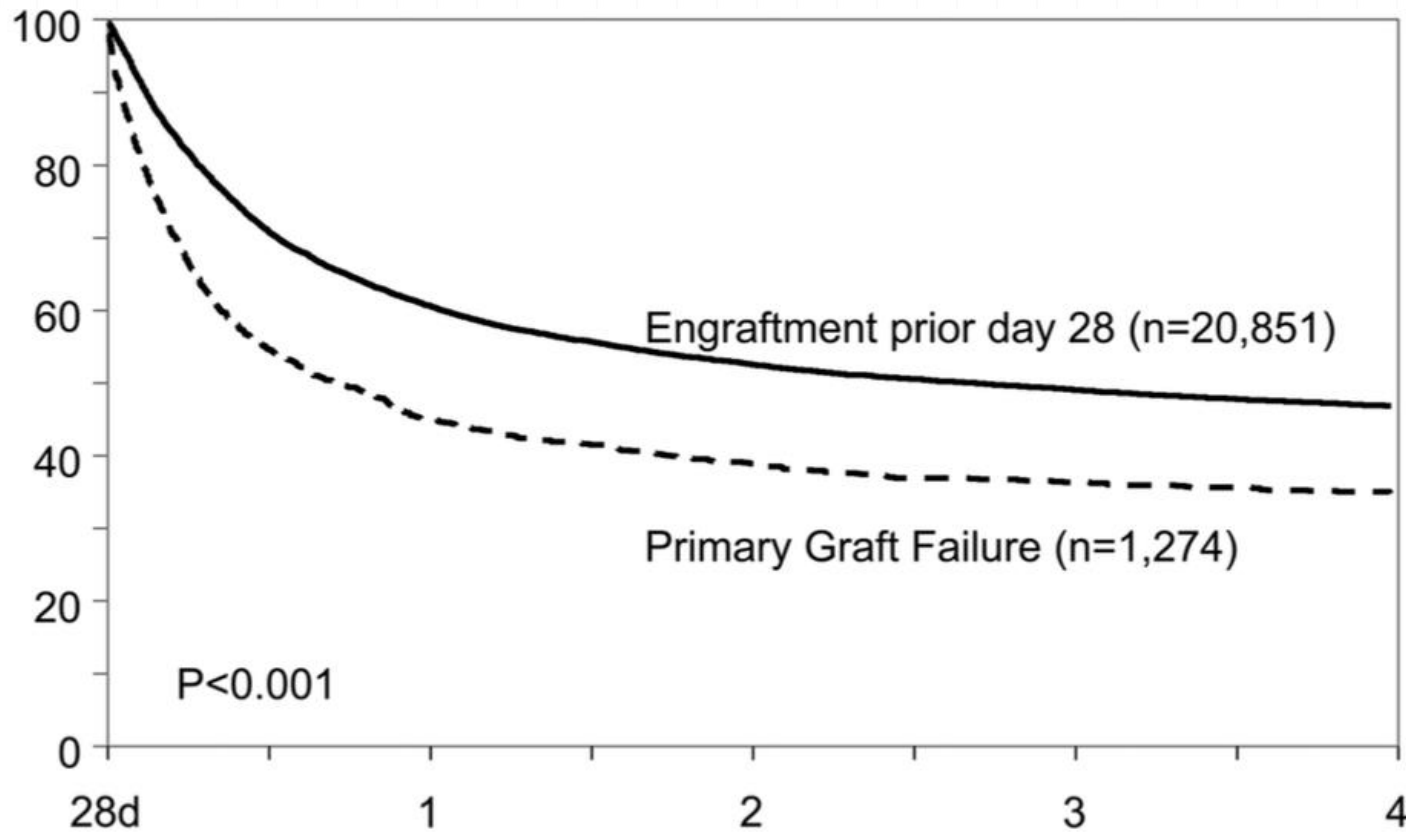
Nakil sonrası 28.günde nötrofil $<0.5 \times 10^9/L$
Kord naklinde 42.gün

Engraftman yetmezliđi?

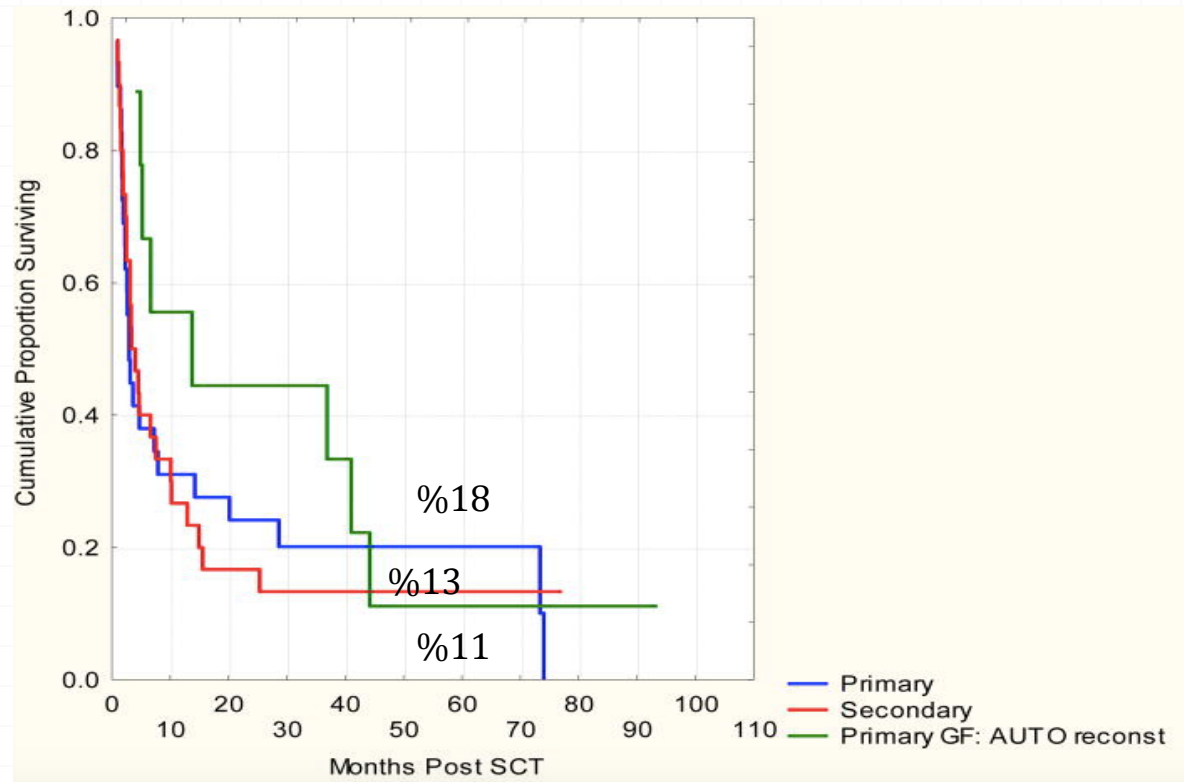
Zayıf graft fonksiyonu?

		Donör engrafman	Hematolojik toparlanma	Sitopeni	Relaps	Kemik iliđi	Kimeriz m
Engrafman yetmezliđi	Primer	Hayır	Hayır	Evet	Hayır	Hiposelüler	Miks veya full alıcı
	Sekonder	Evet	Evet				
Zayıf graft fonksiyonu	Primer	Evet	Hayır	Evet	Hayır	Hiposelüler	Full donör
	Sekonder	Evet	Evet				

Engrafman yetmezliği -sağkalım-

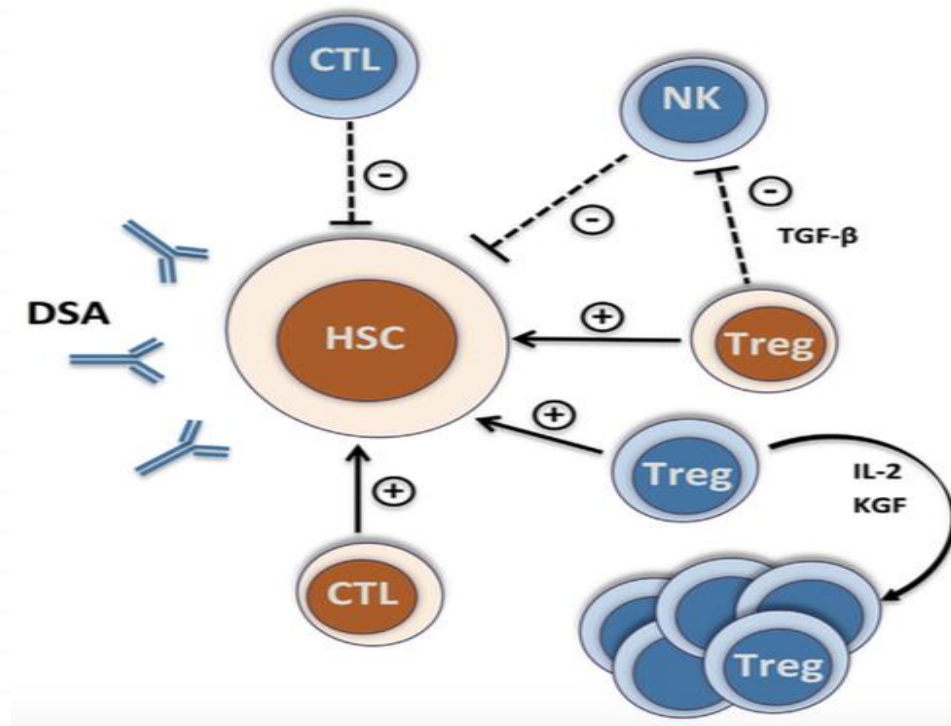


Engrafman yetmezliđi -saękalım-



Rondon G, BBMT 2008

Engrafman yetmezliđi -patogenez-



Engrafman yetmezliđi

-risk faktörleri-

Tanı

Hazırlık rejimi

HLA uyumu

Kök hücre kaynađı

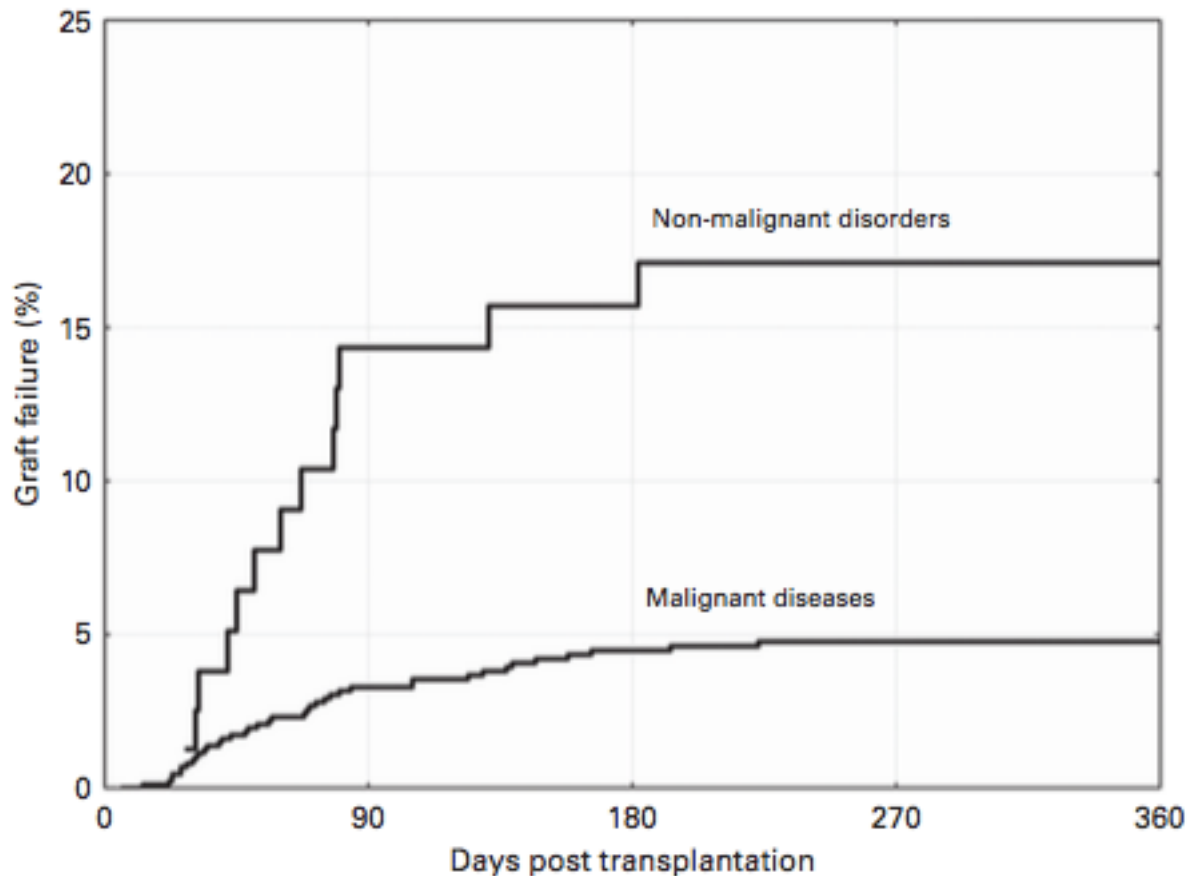
Kök hücre dozu

Kan grubu uyumsuzluđu

Anti HLA antikorları

Engrafman yetmezliği

-Hematolojik tanı-

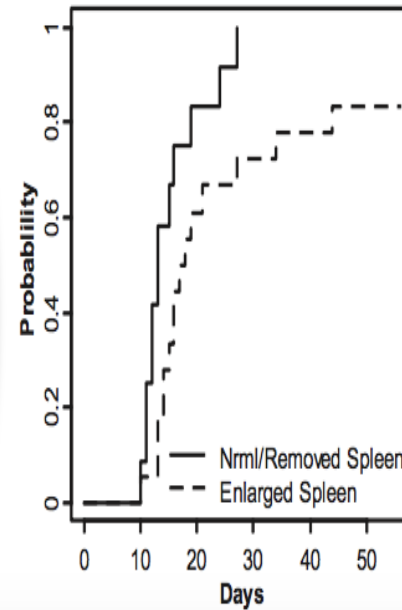


Engrafman yetmezliđi

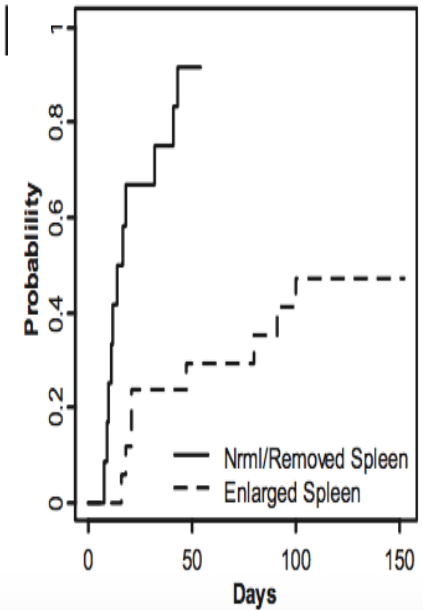
-Hematolojik tanı-

Table 1 Major Published Studies on Hematopoietic Stem Cell Transplantation for Myelofibrosis

Study	n	Follow-Up, Years	OS/RFS/NRM/RR, %	Day 100 Mortality, %	Primary GF, %
Ballen et al ¹ CIBMTR	289	5	MRD 37/33/32/28 URD 30/27/48/23	MRD 18 URD 35	MRD 9 URD 20
Kroger et al, ^{2,a} EBMT	103	5	67/51/16 ^b /29	^c	2
Patriarca et al ³	100	3	42/35/43/41	17	12
Robin et al ⁵	147	4	39/32/39/29	—	10
Scott et al ¹³	170	5	57/57/34/10	—	3.5
Abelsson et al ⁶	92	5	RIC 59/—/23/8 MAC 49/—/45/10	RIC 5.9 MAC 17.5	14
Gupta et al ⁷ CIBMTR	233	5	47/27/24/48	—	3
Alchalby et al ⁸	150	5	60/—/—/—	—	—
Rondelli et al ⁹	66	2 ^d	MRD 75/—/22/9 MUD 32/—/59/9	MRD 9 ^e MUD 50 ^e	MRD 3 MUD 24



Nötr.engfr.

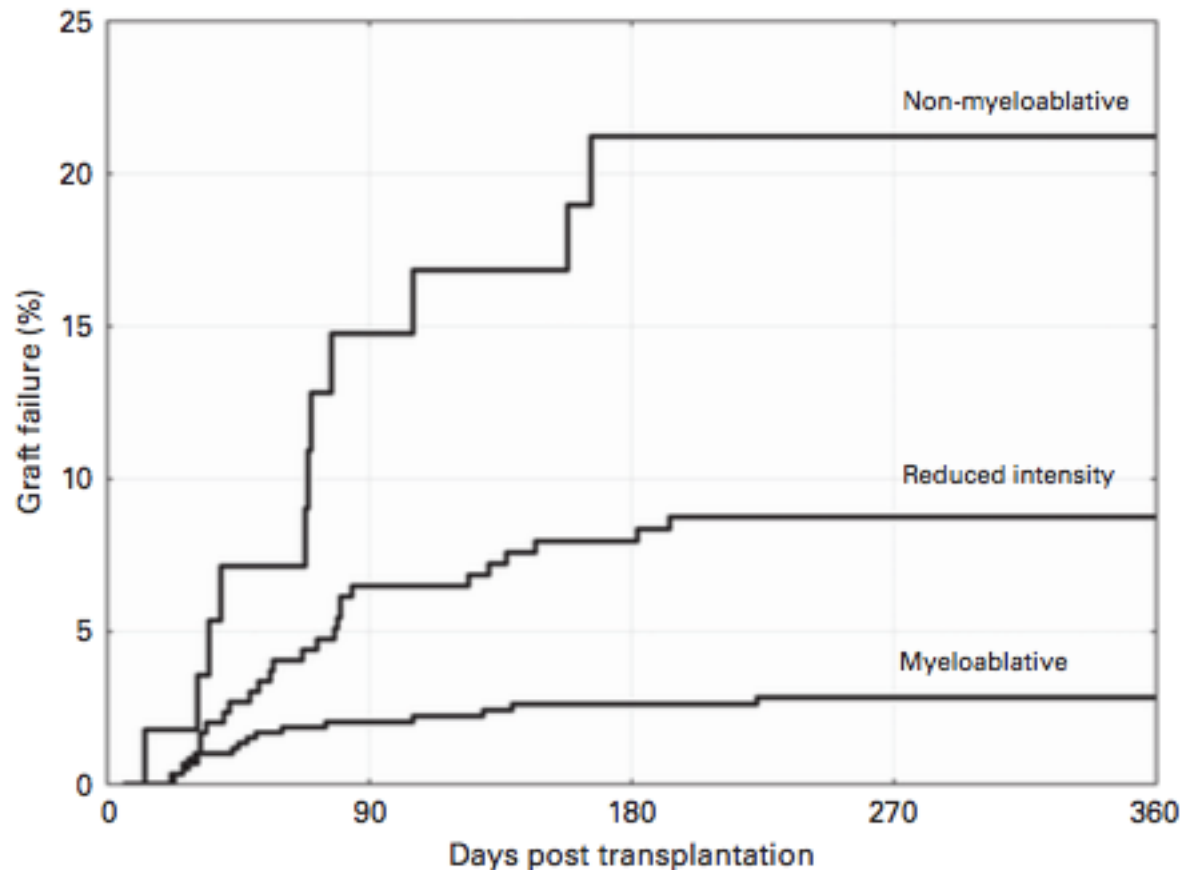


Plt .engfr.

Gergis U,Clin Leuk Lymphoma 2016

Engrafman yetmezliği

-Hazırlık rejimi-



Engrafman yetmezliđi

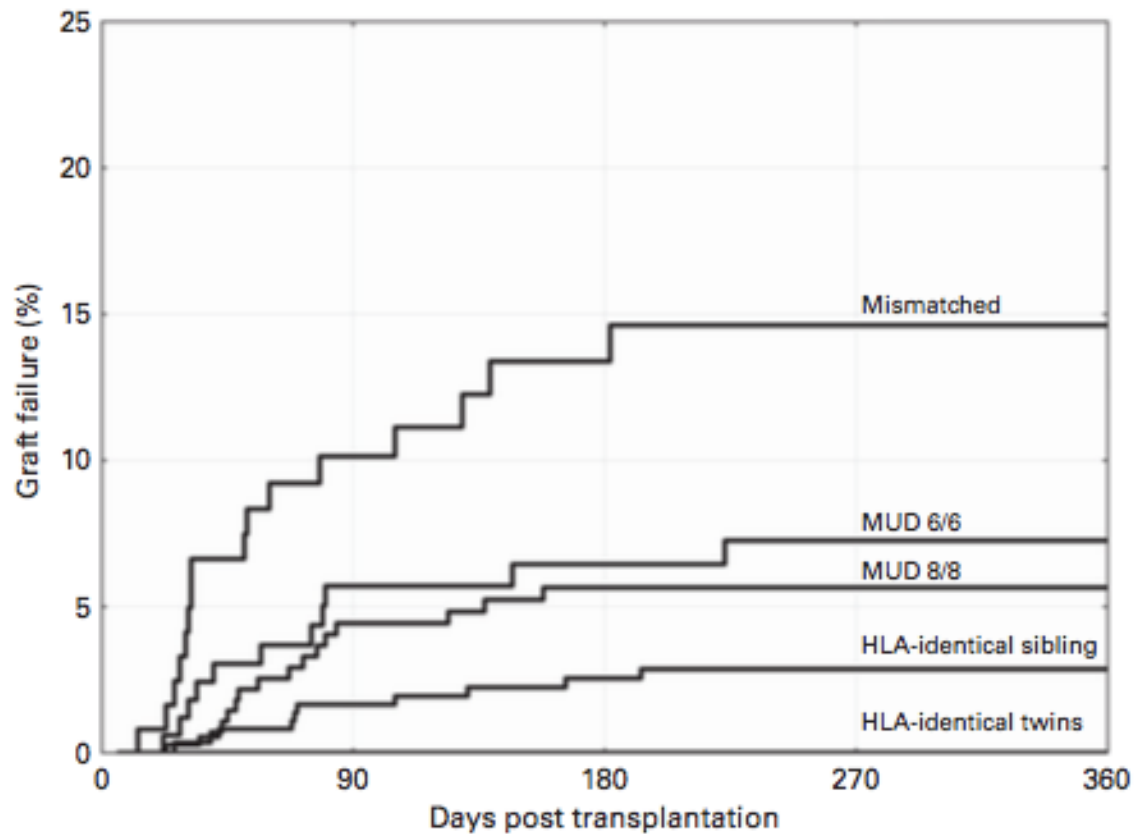
-Hazırlık rejimi-

Myeloablatif nakil;Bu-cy ile risk fazla,Tacrolimus ile risk az

İndirgenmiş Y.nakil; CSA+MMF riski artırır.

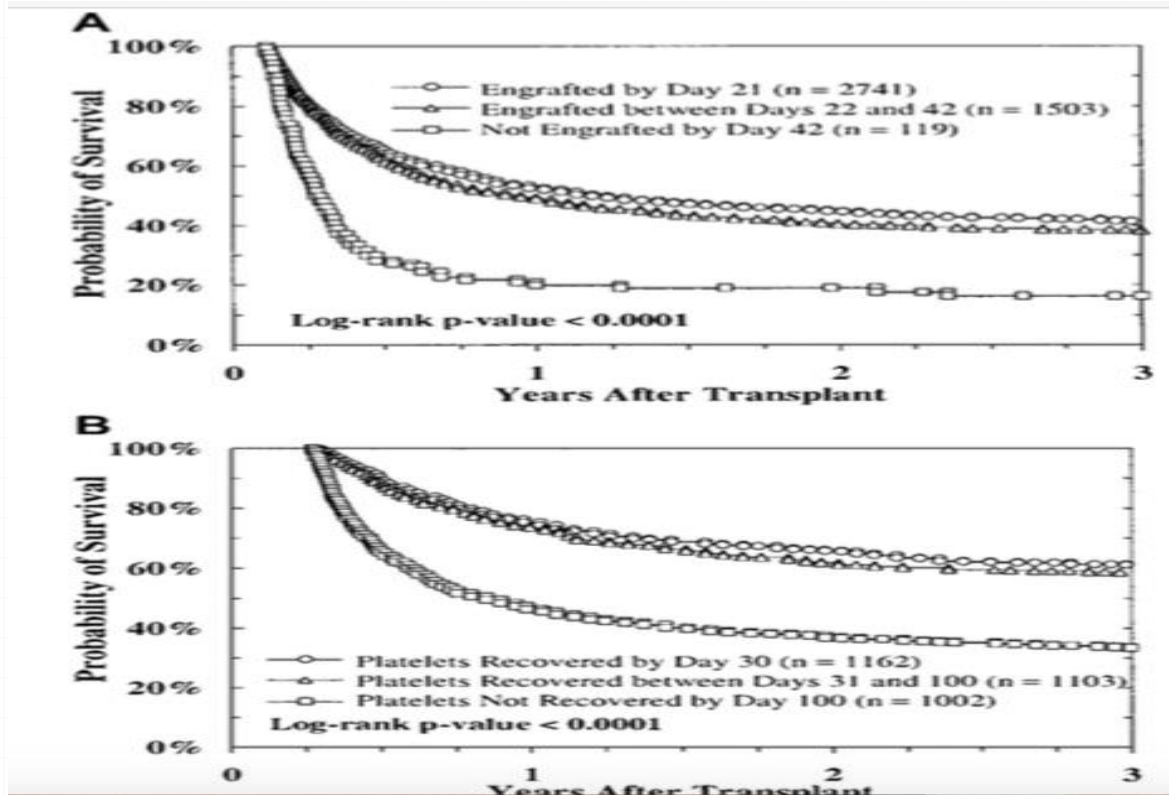
Olson R ,Leukemia 2015
Hagen P,BMT 2014
Finke J,Lancet oncol 2009

Engrafman yetmezliği -HLA uyumu-



Engrafman yetmezliği

-Akraba dışı nakil-



ORIGINAL ARTICLE

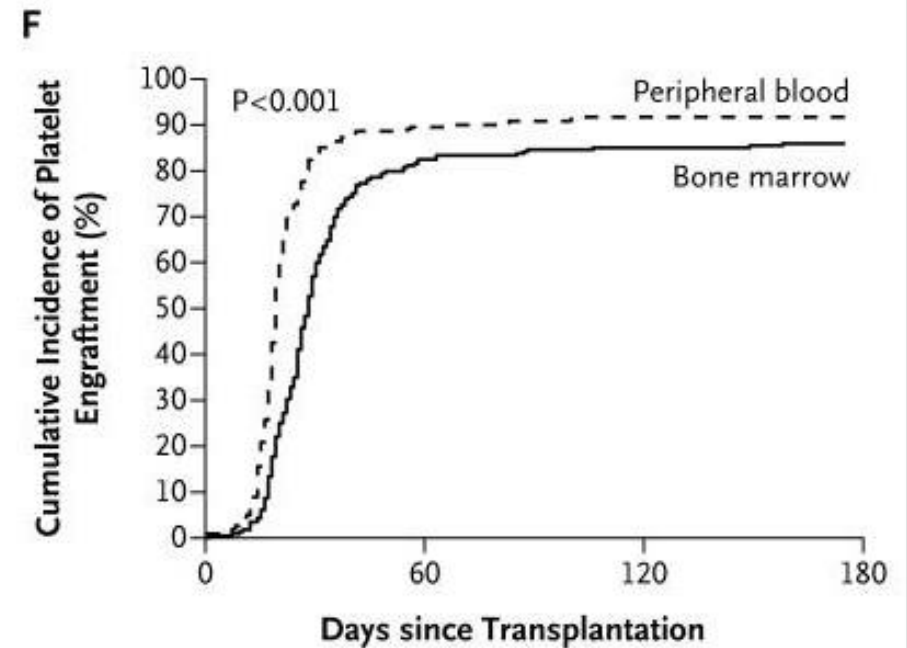
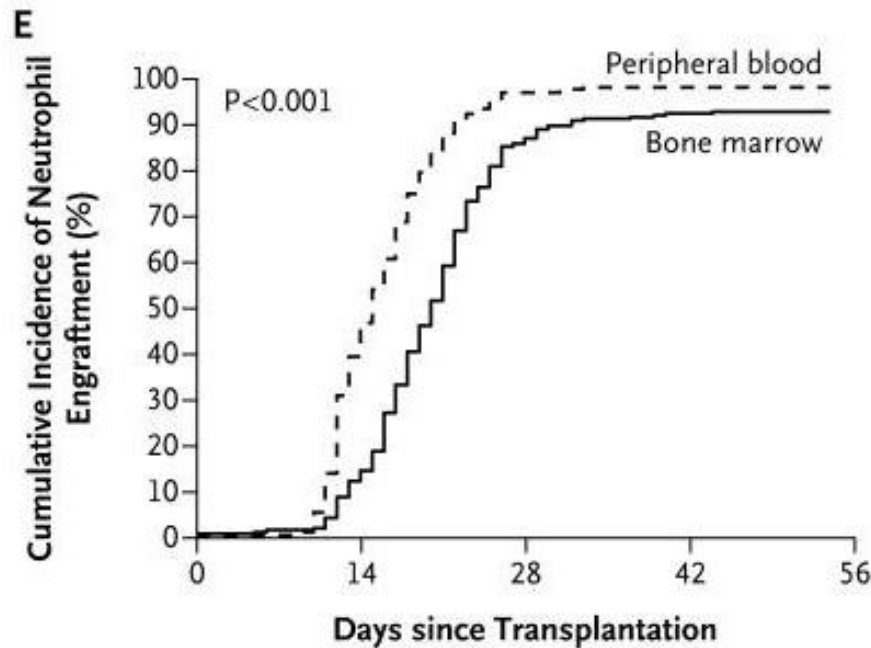
Risk factors and outcome of graft failure after HLA matched and mismatched unrelated donor hematopoietic stem cell transplantation: a study on behalf of SFGM-TC and SFHI

T Cluzeau^{1,2}, J Lambert³, N Raus⁴, K Dessaux³, L Absi⁵, F Delbos⁶, A Devys⁷, M De Matteis⁸, V Dubois⁹, M Filloux¹⁰, M Fort¹¹, F Hau¹², I Jollet¹³, M Labalette¹⁴, D Masson¹⁵, B Mercier¹⁶, B Pedron¹⁷, P Perrier¹⁸, C Picard¹⁹, F Quainon²⁰, A Ramounau-Pigot²¹, V Renac²², P Van Endert²³, D Charron²⁴, R Peffault de la Tour²⁵, JL Taupin²⁶ and P Loiseau^{24,27}

	Engraftment, N = 2543	Graft failure, N = 103	P-value
	N (%)	N (%)	
Sex			
Men	1536 (95.8%)	67 (4.2%)	0.36
Women	1007 (96.5%)	36 (3.5%)	
Disease			
Non-malignant	168 (96.3%)	11 (6.1%)	0.04
Lymphoid	1325 (93.9%)	61 (4.4%)	
Myeloid	1041 (97.1%)	31 (2.9%)	
NA	9	0	
Status of disease in malignant disease			
CR	1779 (97.6%)	44 (2.4%)	< 0.0001
No CR	587 (92.4%)	48 (7.6%)	
Type of CR			
CR1	1138 (96.4%)	43 (3.6%)	0.61
CR2 or more	1405 (95.9%)	60 (4.1%)	
Conditioning regimen			
MAC	1441 (95.6%)	66 (4.4%)	0.16
RIC	1094 (96.7%)	37 (3.3%)	
NA	8	0	
Stem cell source			
BM	785 (96.3%)	30 (3.7%)	0.83
PSC	1754 (96.1%)	72 (3.9%)	
NA	4	1	
Sex matching			
Others	2066 (96.2%)	81 (3.8%)	0.52
Woman in man	460 (95.6%)	21 (4.4%)	
NA	17	1	
ABO matching			
Compatibility	1193 (96%)	50 (4%)	0.92
Minor incompatibility	658 (96.1%)	27 (3.9%)	
Major incompatibility	692 (96.4%)	26 (3.6%)	
HLA matching			
Matched unrelated	1473 (95.7%)	66 (4.3%)	0.22
Mismatched unrelated	1070 (96.7%)	37 (3.3%)	
GVHD prophylaxis			
Ciclosporine alone	477 (97.3%)	13 (2.7%)	0.076
Ciclosporine/	1031 (96.3%)	40 (3.7%)	
Methotrexate	661	18	
Ciclosporine/MMF	930 (95.8%)	41 (4.2%)	
Others	105 (92.1%)	9 (7.9%)	
Median of infused total nucleated cell dose			
10 ⁸ /kg	1849	58	0.52
	7 [3;10] (1;29)	7 [4;10] (1;27)	
BM	566	14	0.88
	2 [1;4] (1;19)	2.5 [1.25;3] (1;9)	
PSC	1283	44	0.88
	8 [6;12] (1;29)	8 [6;11.25] (3;27)	
Median CD34+ cell dose			
10 ⁶ /kg	2194	78	0.12
	5 [3;8] (1;29)	6 [4;8] (1;24)	
BM	661	18	0.23
	3 [2;4] (1;27)	2 [1;3] (1;12)	
PSC	1533	60	0.11
	6 [5;8] (1;29)	7 [5;8] (2;24)	

Engrafman yetmezliđi

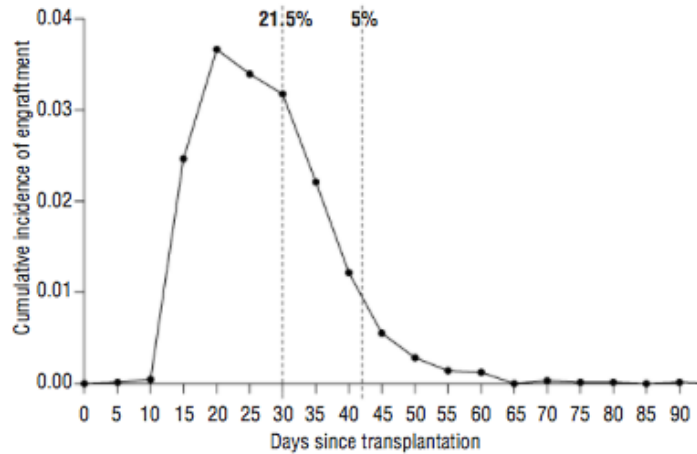
-Kök hücre kaynađı-



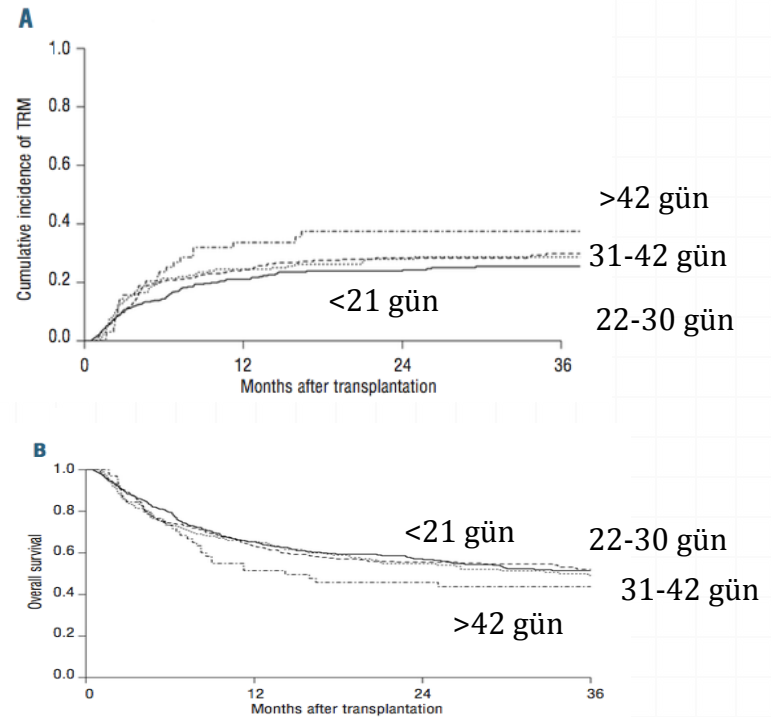
Primer graft yetmezliđi PK ile %2 vs K.İ 6%
Sekonder graft yetmezliđi PK ile %1 vs % 3

Engrafman yetmezliği -Kök hücre kaynağı-

Kordon kanı ile %15 'e varan GY



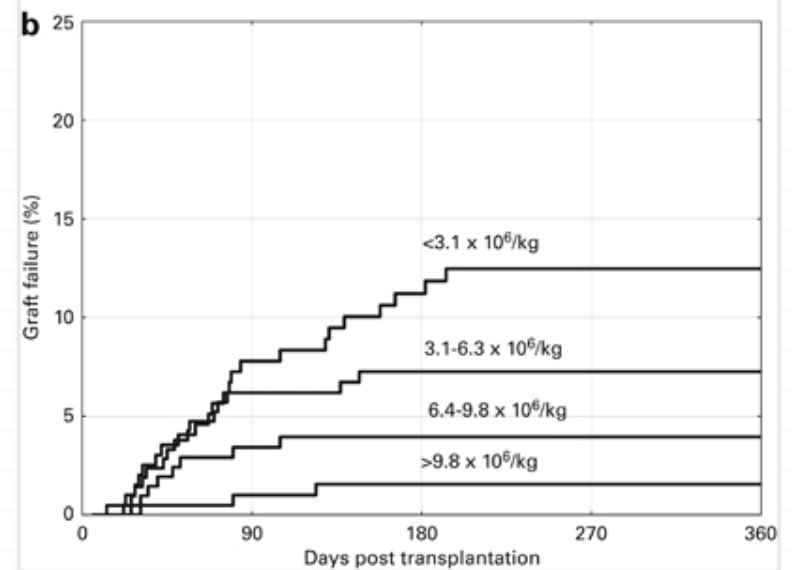
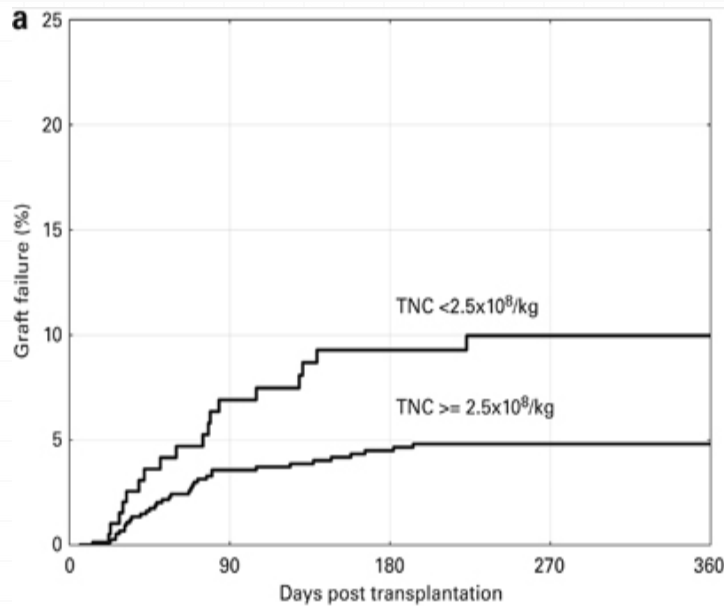
Kordon nakli engrafman kinetiği



Baron F, Oncotarget 2016
Ruggeri A, Hematologica 2014

Engrafman yetmezliği

-Kök hücre dozu-



Olson R,BMT 2013

Engrafman yetmezliđi

-Kordon naklinde kök hücre dozu-

Çift kordon nakli

Ex vivo ekspansiyon

Kemik içi injeksiyon

Kord+Haploidentik nakil

Kord+NK hücre infüzyonu

Beksac M,front mED 2016

Rocha V,Transpl.2013

Liu H,Blood 2011

Engrafman yetmezliđi -Haploidentik nakil-

MEGA DOZ CD34+ HÜCRE İNFÜZYONU

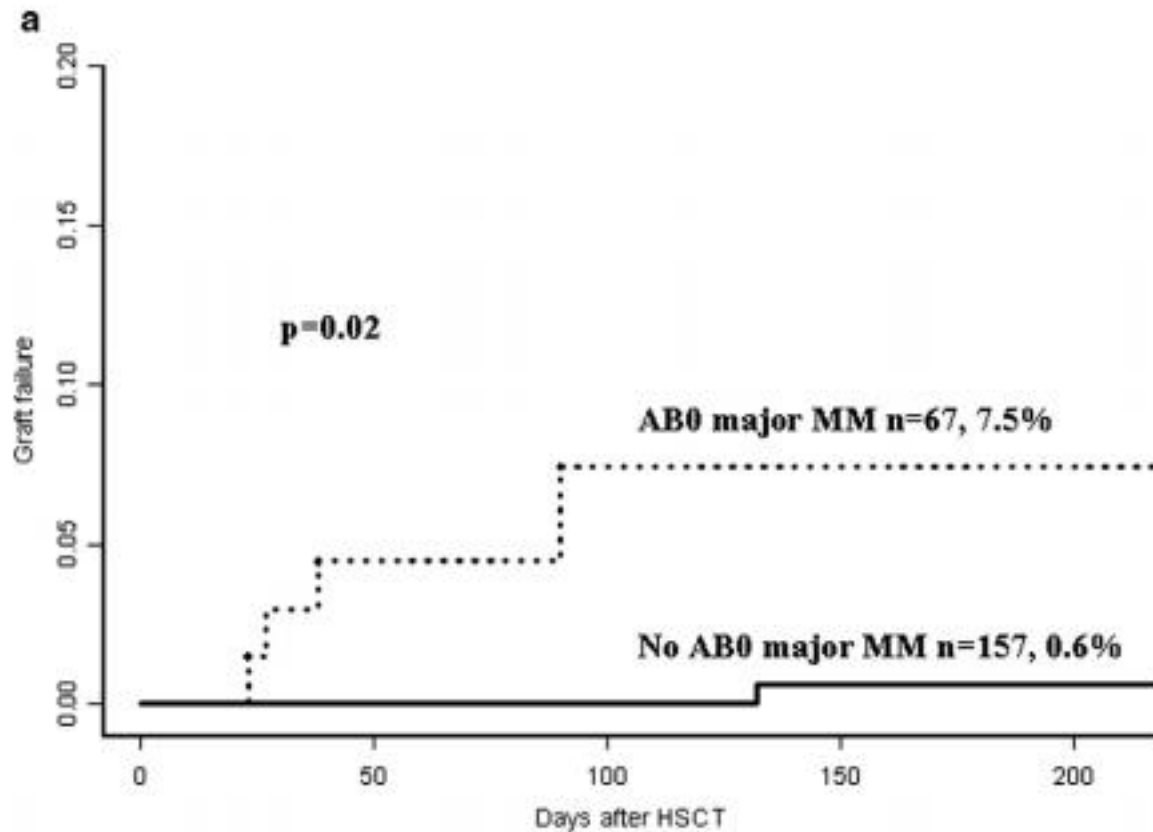
In vivo T HÜCRE DEPLESYONU

MA+ATG+GCSF PRIMED P.KÖK HÜCRE

POSTTRANSPLANT CY

Rizzeri DA,JCO 2007
Huang xj,BBMT 2009
Raiola AM,BBMT 2013

Engrafman yetmezliği -ABO uyumsuzluğu-



Engrafman yetmezliği

-Anti-HLA antikorları-

- ◊ Kadınlarda erkeklerden daha fazla
- ◊ Anti HLA class 1 ve anti DQ önemli.
- ◊ Anti HLA DP??

Ruggeri A,Haematologica 2013
Ciura os,transplant. 2009

Engrafman yetmezliği

-Anti-HLA antikorları-

Reference	Patients (n)	Stem cell source	Conditioning	Anti-HLA%	DSA%	Graft failure with/without DSA
Spellman et al. (34)	115	Mismatched unrelated	RIC	ND	9	24 versus 1%
Ciurea et al. (36)	592	10/10 and 9/10 unrelated	MACorRIC	19.6	1.4	37.5 versus 2.7%
Yoshinara et al. (39)	79	Haplo-identical	RIC	20.2	14	27 versus 3%
Ciurea et al. (36)	24	Haplo-identical	RIC	ND	21	60 versus 5%
Chang et al. (40)	345	Haplo-identical	MAC	25.2	11.3	61% (MFI, 10,000) versus 3.2%
Ciurea et al. (36)	122	Haplo-identical	Non-specified	ND	18	32 versus 4%
Takanashi et al. (41)	386	Single CBU	MAC	23.1	5	83 versus 32%
Cutler et al. (42)	73	Double CBU	MACorRIC	ND	24	57 versus 5.5%
Ruggeri et al. (43)	294	Single and double CBU	RIC	23	5	81 versus 44%
Yamamoto et al. (44)	175	Single CBU	MACorRIC	39.4	ND	50% if anti-HLA-C, DP, DQ, DRB1/2/3 versus 16%

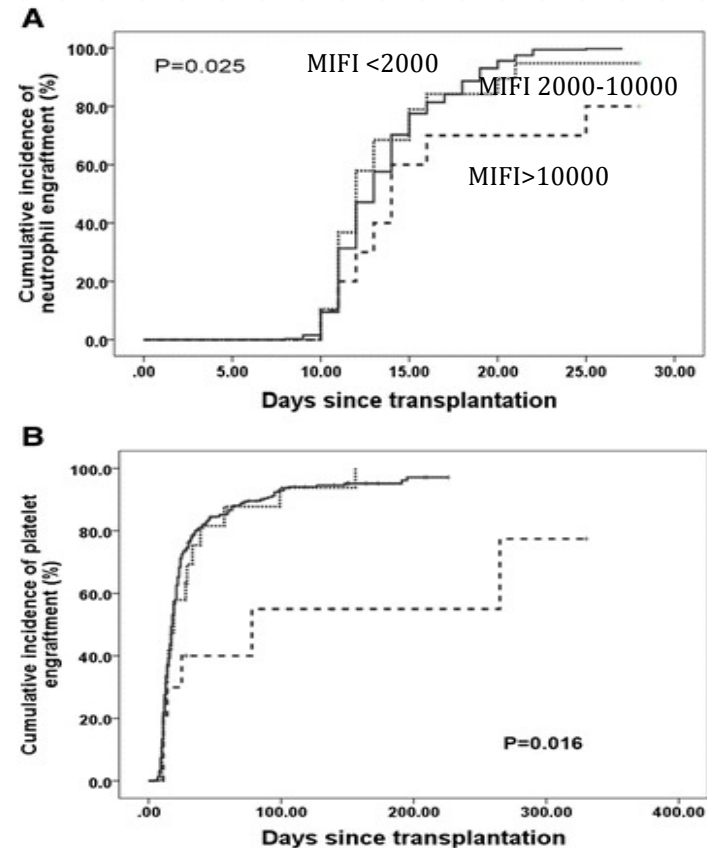
AÜTF Deneyimi

n	44
Ortanca yaş	46(21-67)
Cinsiyet(E/K)	24/20
<u>Primer</u> hastalık(AML/ALL/ <u>Aplastik</u> anemi/MDS /KML/ <u>Myelofibrozis</u> / <u>Lenfoma</u> / <u>Myeloma</u>)	17/11/6/1/2/4/2/1
Hazırlık rejimi	
Ablatif	33
Azaltılmış yoğunluklu	11
Kök hücre kaynağı	
<u>Periferik</u> kan	36
Kemik iliği	8
HLA uyumu	
Tam uyumlu	26
Bir HLA uyumsuz	10
<u>Haploidentik</u>	8
Anti HLA antikorı(var/yok)	27/17
DSA(var/yok)	3/41
<u>Engraftman</u> yetmezliği(var/yok)	7/37

Engrafman yetmezliđi

-Anti-HLA antikorları-

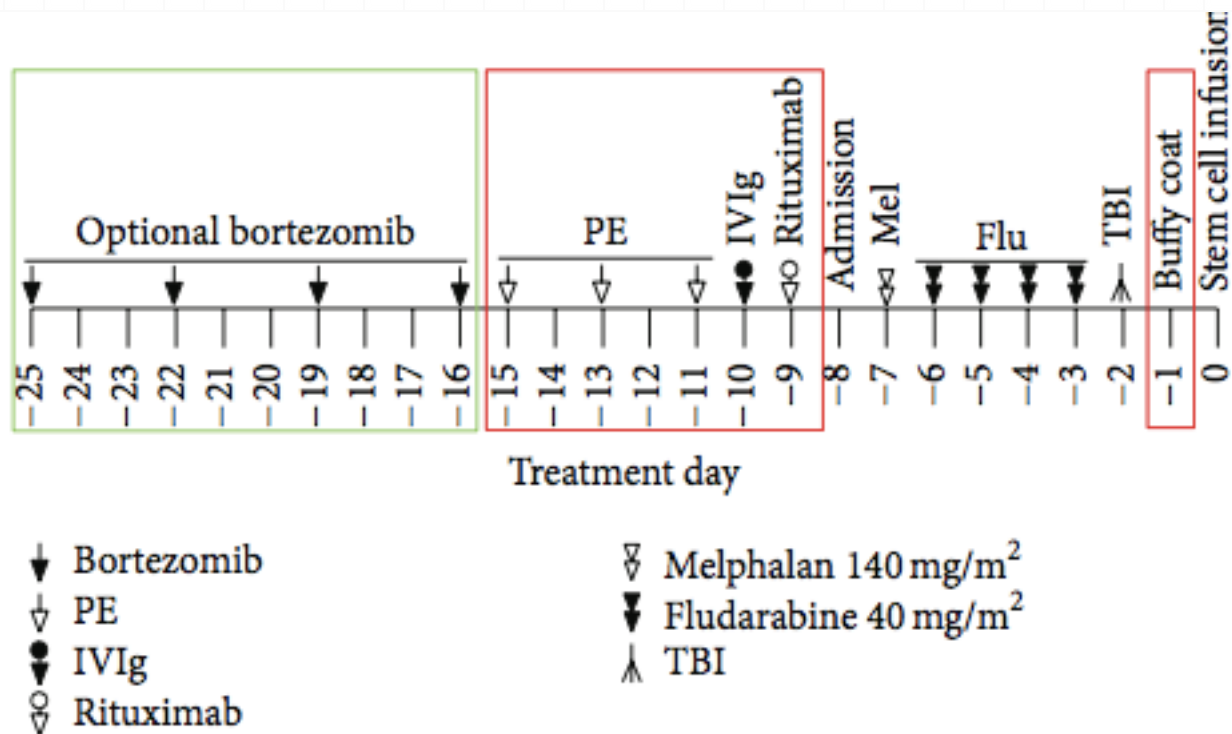
- ◊ Kompleman ilişkili sitotoksisite
- ◊ Single antigen flow Bead
- ◊ Mean flörosan intensitesi(MFI);cut off?
- ◊ MFI titre ile nakil sonrası ab persistansı ilişkili olabilir.



Engrafman yetmezliđi -Korunma-

Reference	Donor type (N)	Anti-HLA abs test	Desensitization method	MFI after treatment	Graft outcome
Barge et al. 1989 [41]	Haplo (N = 1)	CDC	Plasmapheresis	NA	Graft failure
Maruta et al. 1991 [52]	Mismatched related (N = 1)	AHG-CDC	CyA, methylpred, Plasmapheresis, DLI	Negative XM	Engrafted
Braun et al. 2000 [53]	Haplo (N = 1)	FCXM	Staphylococcal protein A immunoadsorption	Negative XM	Engrafted
Ottinger et al. 2002 [20]	Mismatched related (N = 2)	DTT-CDC	Plasmapheresis, mismatched platelet transfusion	1 patient with negative XM, 1 patient with positive XM	Patient with negative XM after treatment engrafted, while patients with positive XM had GF
Pollack and Ririe 2004 [54]	Mismatched HLA-A68 related (N = 1)	FCXM	Platelet transfusion, plasmapheresis, IVIg	Negative XM	Engrafted
Narimatsu et al. 2005 [55]	Mismatched related (N = 1)	AHG-LCT	Rituximab, platelet transfusion	Negative AHG-LCT	Engrafted
Ciurea et al. 2009 [22]	Haplo (N = 4)	Luminex MFI >500	Rituximab, plasmapheresis	1 negative, 1 low titer, 2 high titers	Patients with DSAs negative and low titer after treatment engrafted; 2 patients with high titer had GF
Yoshihara et al. 2012 [48]	Haplo (N = 5)	Luminex MFI >500	Plasmapheresis + rituximab (N = 2), platelet transfusion (N = 2), bortezomib + dexamethasone (N = 1)	1 patient had temporary DSA reduction and 1 patient had significant reduction after plasmapheresis; 2 patients had a significant reduction post platelet transfusion; 1 patient had moderate DSA reduction after bortezomib and dexamethasone	All patients engrafted
Ciurea et al. 2015 [46]	Haplo (N = 12)	Luminex MFI >500	Plasmapheresis + rituximab + IVIg (N = 5), PE + rituximab + IVIg + donor buffy coat infusion (N = 7)	No significant change of MFI before transplant. All patients cleared DSA after transplant	5 patients with C1q positive after treatment had GF while patients who became C1q negative engrafted
Leffell et al. 2015 [56]	Haplo (N = 13) MMUD (N = 2)	Luminex MFI >1000	Plasmapheresis + IVIg	Mean reduction of DSAs after treatment was 64.4%. 1 patient failed to reduce DSAs to the level that was thought to be safe for transplant	All 14/14 transplanted patients engrafted

Engrafman yetmezliği -Korunma-



Engrafman yetmezliği predikte edilebilir mi?

Day 21 weighted PGF risk scores	Score
Recipient age	
≥30 years	0
<30 years	1
Karnofsky/Lansky score	
≥90%	0
<90%	1
Disease	
AML	0
ALL	0
MDS	1
CLL	2
CML	2
MPD ^a	3
Disease status ^b	
Other	0
Advanced AML/ALL/CML	1
HLA match status ^c	
HLA identical sibling	0
Well matched unrelated	0
Partially matched unrelated	0
Mismatched unrelated	2
Graft type/total nucleated cell dose (TNC)	
BM TNC >2.4 × 10 ⁶ /kg	0
BM TNC ≤2.4 × 10 ⁶ /kg	1
Peripheral blood	2
Conditioning regimen	
TBI+/- other	0
Other	2
GVHD prophylaxis	
Calcineurin inhibitor ^d + MTX +/- other	0
Other GVHD prophylaxis	3
T-cell depletion	4

>7 RİSKLİ

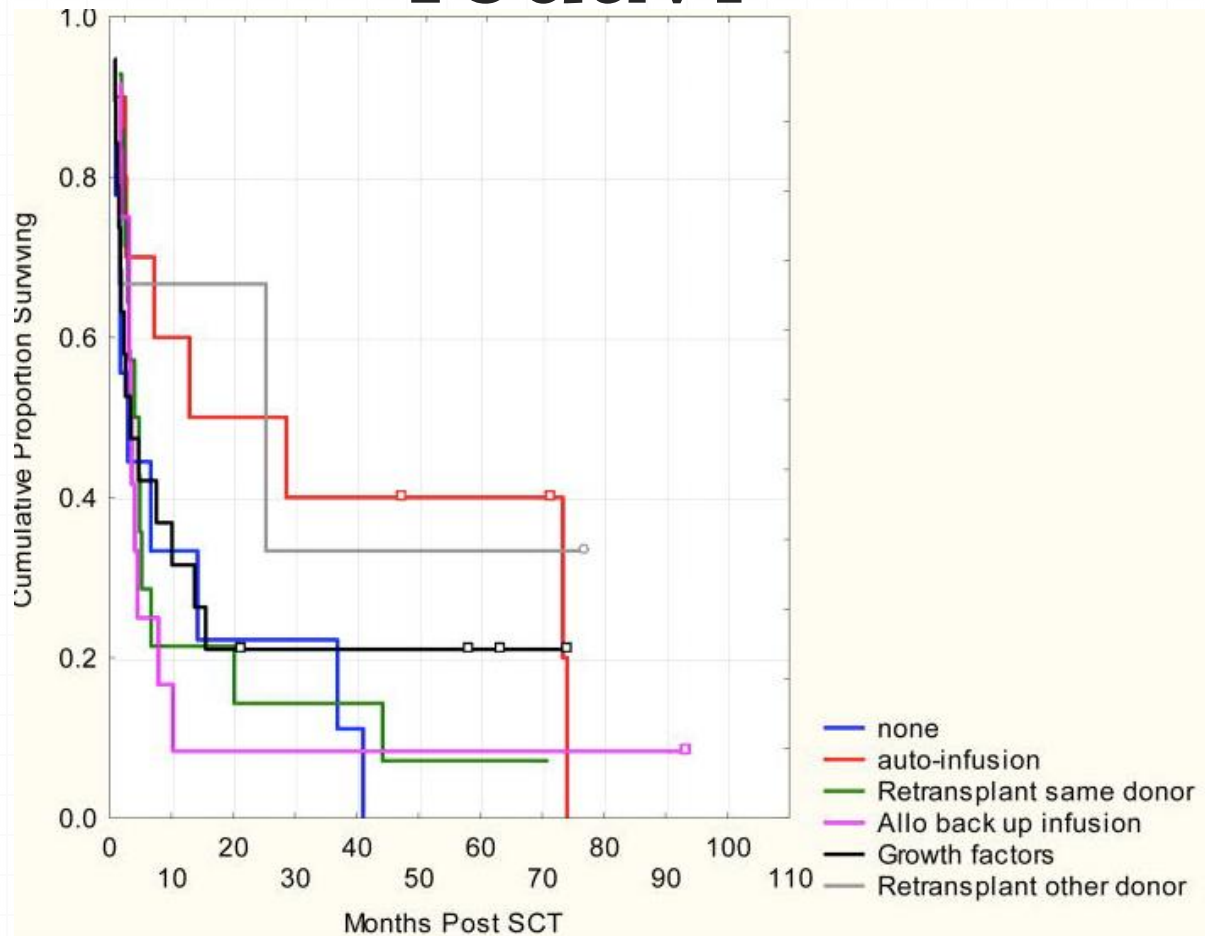
Engrafman yetmezliği

-Tedavi-

3.haftada hematolojik toparlanma olmayan hasta;

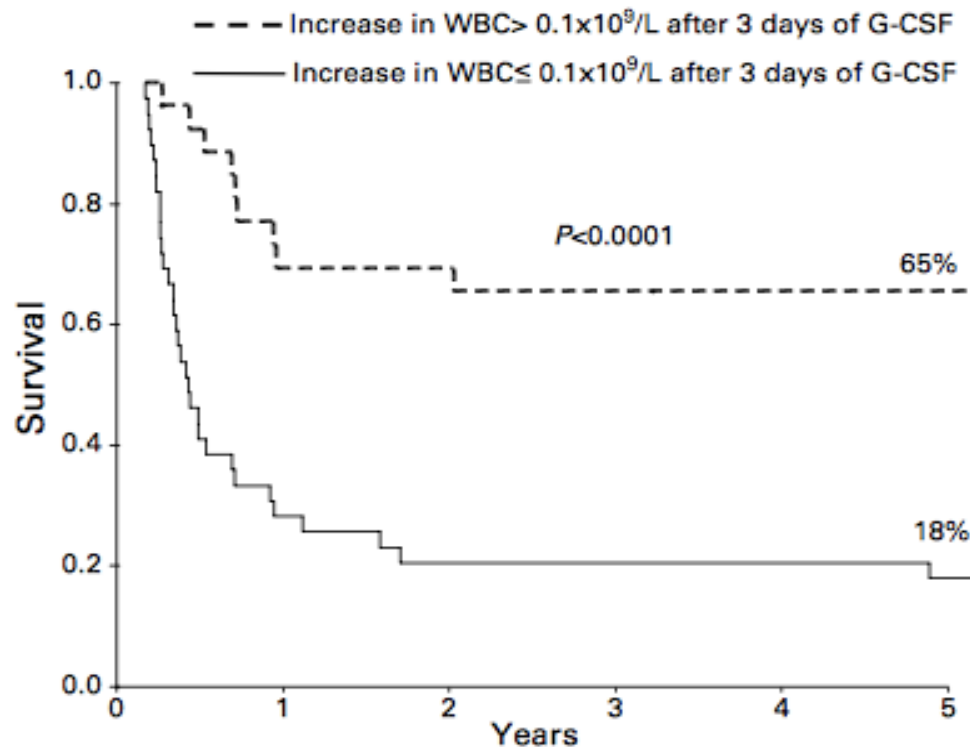
- potansiyel kök hücre toksik ilaçları kes
- aktif hastalık ve viral infeksiyon etkilerine yönelik Kİ.yap
- GCSF başla
- 28.gün;plan yap

Engrafman yetmezliđi -Tedavi-

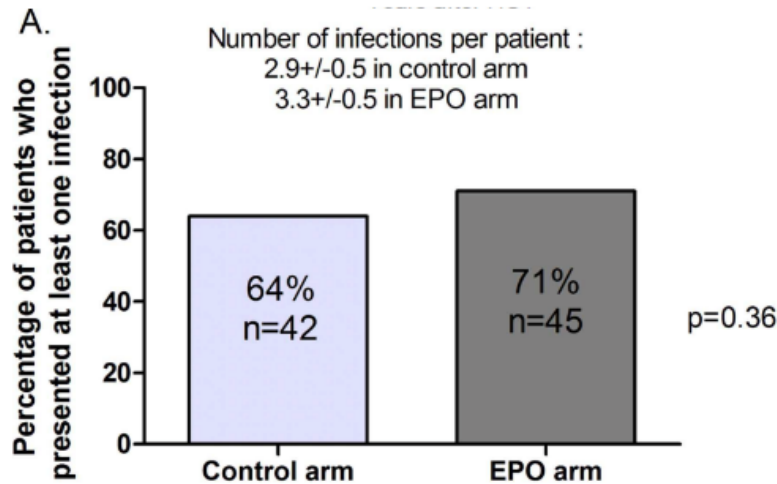


Engrafman yetmezliği

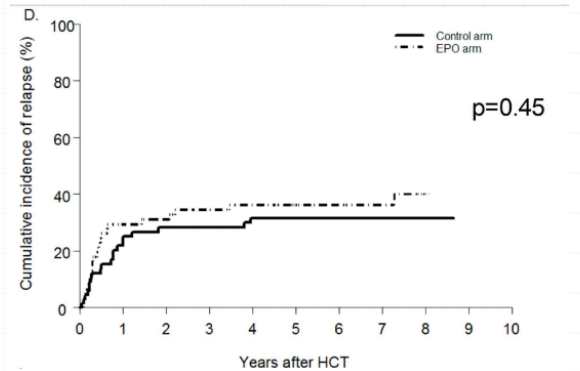
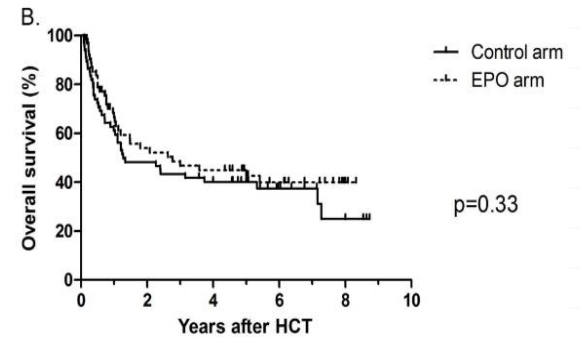
-Tedavi/GCSF-



Engrafman yetmezliđi -Tedavi/EPO



28.Günden sonra kullanımında trihtiyacı azalır.
500 u/kg/hafta
Yan etki profili artmaz.



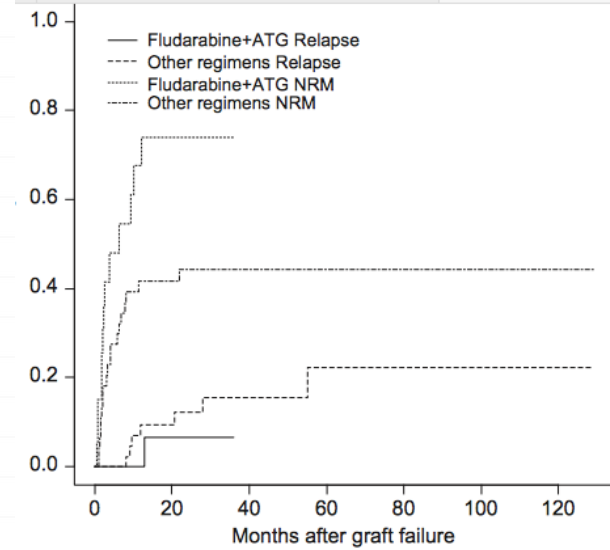
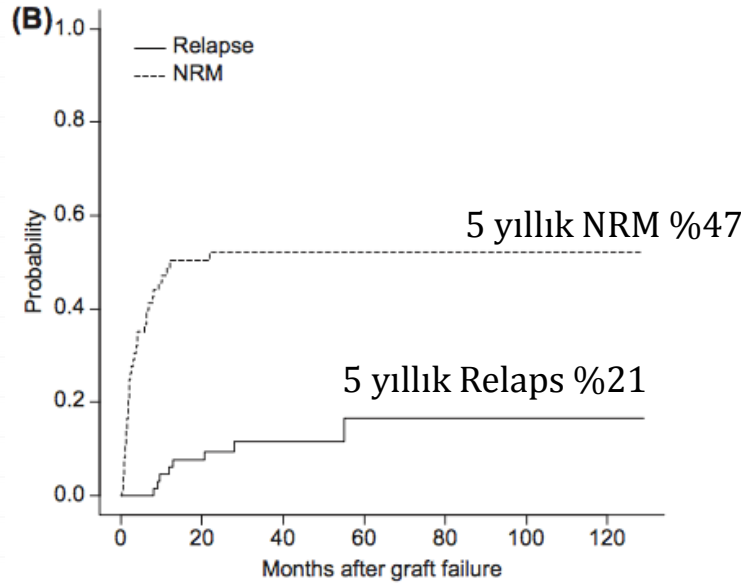
Jaspers A,Blood 2014
Jaspers A,Am J Hematol 2015

Engrafman yetmezliği

-Tedavi/TP0 agonistleri-

- Eltrombopag,12 hasta
- Uzamış trombositopenide %60 başarı.
- Sekonder trombositopenide %71 başarı.
- K.iliği megakaryosit sayısı yanıtı belirler.
- Yan etki nedeni ile tedaviyi bırakan yok.

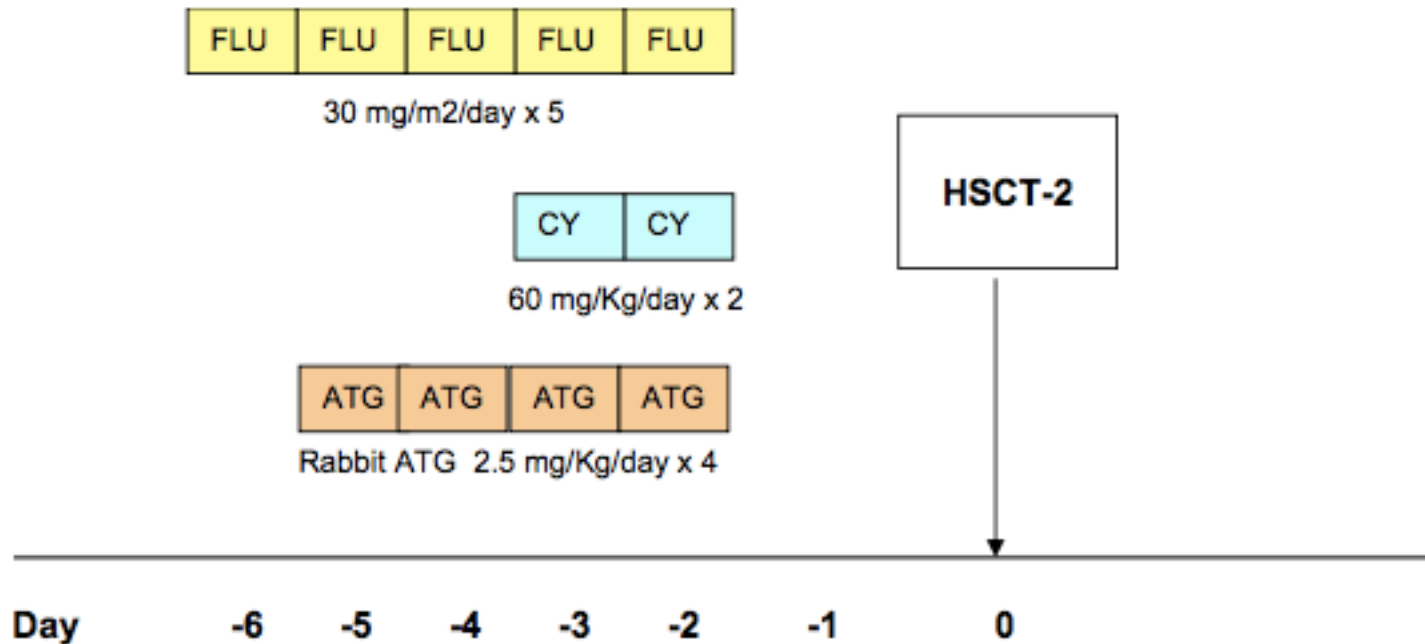
Engrafman yetmezliđi -2.nakil-



GF sonrası ortanca sağkalım 12 ay.
5 yıllık sağkalım %31.

Fludarabine-Based Conditioning Secures Engraftment of Second Hematopoietic Stem Cell Allografts (HSCT) in the Treatment of Initial Graft Failure

Joseph H. Chewing, Hugo Castro-Malaspina, Ann Jakubowski, Nancy A. Kernan, Esperanza B. Papadopoulos, Trudy N. Small, Glenn Heller, Katharine C. Hsu, Miguel A. Perales, Marcel R.M. van den Brink, James W. Young, Susan E. Prockop, Nancy H. Collins, Richard J. O'Reilly, Farid Boulad



-20 yaş altında sonuçlar daha iyi.

Engrafman yetmezliği

-2.nakil akraba dışı -

- o 122 akraba dışı nakil
- o 24 farklı vericiden,98 aynı vericiden nakil
- o 30 ve 100 günlük mortalite %39 ve %75.
- o 1 yıllık genel sağkalım %11 (10 hasta)
- o Vericiye veya taze/dondurulmuş ürün kullanımına göre fark görülmemiş.

Engrafman yetmezliği

-Kordon nakli sonrası 2.nakil-

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T Cell–Depleted Related HLA-Mismatched

Peripheric Blood Stem Cell Transplantation. [Am J Hematol. 2014 Dec;89\(12\):1097-101. doi: 10.1002/ajh.23845. Epub 2014 Sep 26.](#)

as Salvage Single Transplantation. **Outcomes and management strategies for graft failure after umbilical cord blood transplantation.**

Blood 123:1097-101. Singh H¹, Nikiforow S, Li S, Ballen KK, Spitzer TR, Soliffer R, Antin JH, Cutler C, Chen YB.

Federico  Author information

Miguel A
Pilar Solís

Hematology De

Article history:
Received 7 Feb
Accepted 19 M

Key Words:
Haploidentical
Cord blood tra
Graft failure
T cell depletion

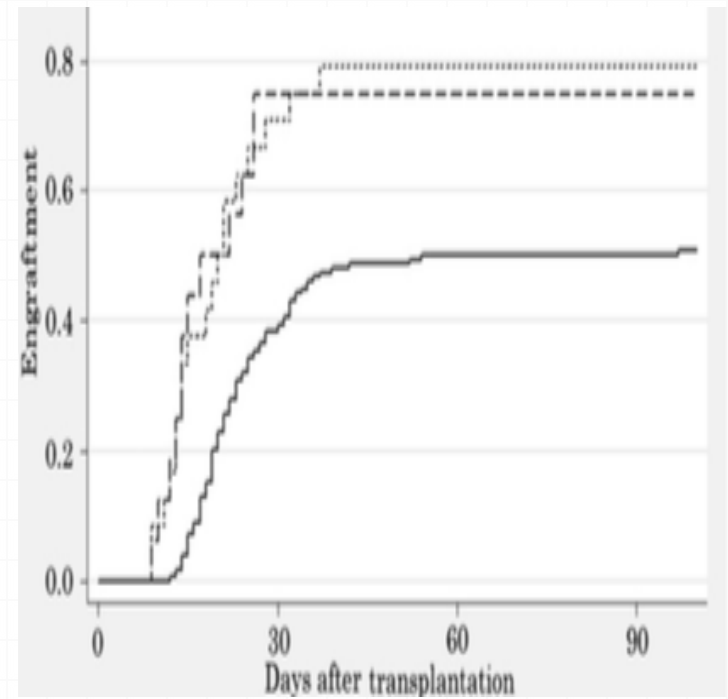
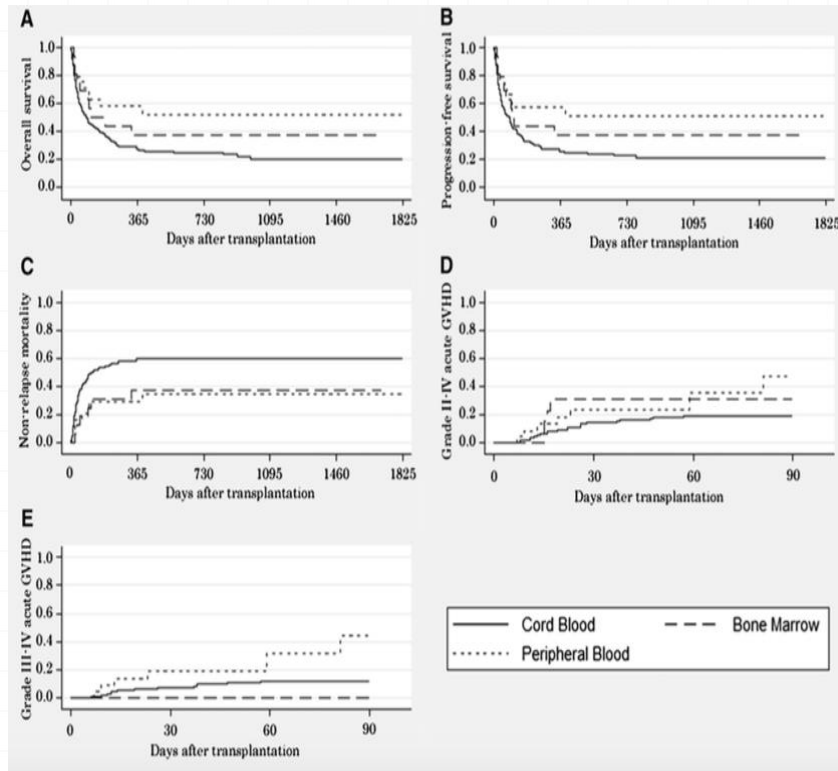
Abstract

Graft failure is a life-threatening complication after allogeneic hematopoietic stem cell transplantation (HSCT). Graft failure is more prevalent after umbilical cord blood transplantation (UCBT) compared with conventional adult stem cell sources. We identified 21 consecutive patients who experienced graft failure after UCBT at our center between 2004 and 2013 and describe their treatment strategies and outcomes. Two patients experienced early death. Seven patients had return of autologous hematopoiesis including 1 patient who was given previously collected autologous stem cells. Twelve patients received a second early HSCT, six from separate UCB units and six from a haploidentical donor. With a median follow-up of 33.2 months for surviving patients, 3-year PFS is 23% and 3-year OS is 37%. Of the six long-term survivors without relapse, four received a second HSCT from a haploidentical donor with post-HSCT high-dose cyclophosphamide based GVHD prophylaxis. This strategy appears safe and merits further investigation in this setting.

—depleted PBSCT is a feasible alternative for treating graft failure after UCBT.

Engrafman yetmezliđi

-Kord nakli sonrası 2.nakil periferik kandan olmalı-



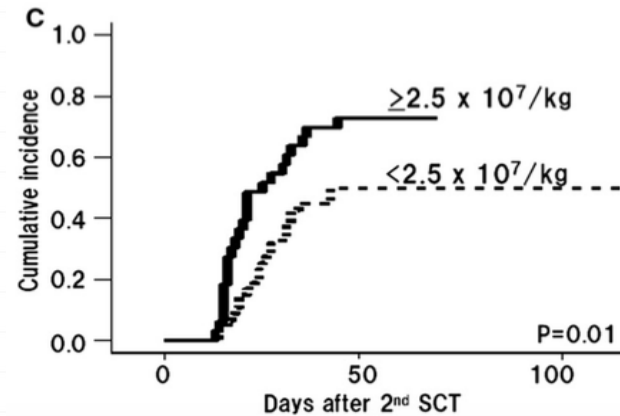
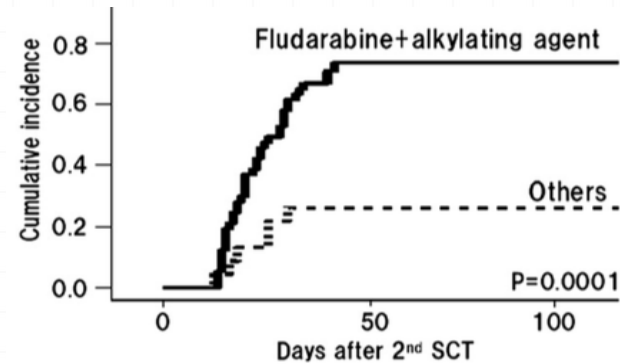
Fuji S,BBMT 2012

Engrafman yetmezliđi

2.nakil kordon kanı ile olacaksa...

- 1 yıllık genel sađkalım %33
- 100 gün mortalite %45.

-İlk nakildeki hastalık statusu ve grade 3-4 organ toksisitesi artmış ölüm riski ile ilişkilidir.



Engrafman yetmezliği

-Kurtarma tedavisi olarak haplo-

Patient no.	Interval from the failed SCT to salvage SCT (days)	Salvage transplantation						
		Donor		HLA match		Preparatory conditioning		CD34 ($\times 10^6$ /kg)
		Same as the failed SCT	Relation	GVH vector	HVG vector	TBI dose (Gy)	ATG product/total dose (/kg)	
1	25	Yes	Sibling	3/6	3/6	4	TMG/5	7.1
2	37	No	Daughter	4/6	3/6	2	TMG/2 ^a	7.9
3	54	No	Daughter	4/6	3/6	4	ATG-F/10	4.0
4	31	Yes	Sibling	4/6	3/6	4	ATG-F/8	3.1
5	36	No	Mother	4/6	4/6	2	TMG/3	3.5
6	40	No	Daughter	3/6	3/6	3	TMG/3	5.5
7	31	No	Daughter	3/6	3/6	3	TMG/3	2.7
8	100	Yes	Daughter	4/6	3/6	4	TMG/3	5.3

Patient no.	Time to engraftment (days)		GVHD		Relapse	Current status	Cause of death
	Neutrophil	Platelet	Acute	Chronic			
1	10	17	0	No	No	Alive, day 3468	Rupture of carotid artery aneurysm
2	8	97	II	No	No	Dead, day 2395	
3	8	35	0	No	No	Alive, day 936	
4	10	17	0	No	Yes (day 718)	Alive, day 916	
5	10	20	II	No	No	Alive, day 459	GVHD GVHD, leukoencephalopathy
6	9	18	0	No	No	Alive, day 246	
7	11	24	III	NE	No	Dead, day 112	
8	11	NA	III	NE	No	Dead, day 91	

Fu/tiotepa/ATG/TBI

Medyan nötrofil ve trombosit engrafmanı 10 ve 20 gün
5 yıllık sağkalım %75

Engrafman yetmezliđi

-Kurtarma tedavisi olarak haplo-

Case	Days from the 1st transplant	Donor	HLA matching at A, B, DR allele	Relation to the 1st donor	CD34 stem cell dose ($\times 10^6/\text{kg}$)	Days until ANC >500	Engrafted	Acute GVHD	Overall survival from the last SCT (month)	Cause of death
1	91	Haplo	3/6	Different	8	12	Yes	0	Alive (30.0)	N.A.
2	42	Haplo	3/6	Same	19.98	Failure	No, rescued by auto	N.A.	Alive (22.4)	N.A.
3	34	Haplo	4/6	Same	13.66	16	Yes	(1)	Died (1.8)	MOF
4	48	Haplo	3/6	Different	11.79	10	Not tested	(0)	Died (0.4)	Infection
5	35	Haplo	3/6	Different	14.94	14	Yes	0	Alive (11.6)	N.A.
6	30	Haplo	3/6	Same	13.27	26	Not tested	(0)	Died (0.9)	MOF
7	34	Haplo	3/6	Different	11.68	10	Yes	1	Alive (4.2)	N.A.
8	41	Haplo	3/6	Different	Missing	9	Yes	2	Alive (6.8)	N.A.
9	35	Haplo	3/6	Same	10.94	17	Yes	0	Alive (10.7)	N.A.
10	36	Haplo	4/6	Same	9.23	22	Yes	2	Alive (4.2)	N.A.
11	35	MSD	6/6	Same	12.42	12	Initially Yes, but later required boost of CD34 after TBI 2 Gy	0	Alive (18.5)	N.A.

Fu,Cy,alemtuzumab,TBI 1 gün
Ortanca 13.gün engrafman

AÜTF deneyimi

Hasta	Eng.Yetm.	Tanı	Kök hücre	1.transp. hazırlık rejimi	GVHD profilaksi	2.trans. hazırlık rejimi	GVHD prof.	2.NAKİL KÖK HÜCRE	Trans.aras ı süre(days)	2.Trans sonrası eng/ex
1	Primary	MDS	PK	Cy+ATG	CSA+MTX	Flu+TBI	CSA+MTX	K.İ	60	Yok/+
2	Secondary	CMLL	PK	Flu+Bu+ATG	CSA+MMF	Flu+Mel	CSA+MMF	PK	203	Yok/+
3	Primary	MDS	PK	Flu+Bu+ATG	CSA+MMF	Flu+Bu+ATG	N/A	PK	49	Yok/+
4	Primary	AML	PK	TBI+Cy+ATG	CSA+MMF	Flu	CSA+MMF	PK	65	Yok/+
5	Primary	AA	Kİ	Cy+ATG	CSA	Cy+ATG	CSA+MTX	PK	51	Var/-
6	Primary	AA	Kİ	Flu+Cy+ATG	Cy+CSA+MMF	Flu+TBI	CSA+MTX	PK	70	Yok/+
7	Primary	CML	PK	Bu+Cy	CSA+MTX	Bu+Cy	MP+MMF	PK	42	Yok/+
8	Secondary	AA	Kİ	Cy+ATG	CSA+MTX	Cy+ATG	CSA+MTX	PK	94	Yok/+
9	Primary	AML	PK	Cy+TBI	CSA+MTX	Bu+Cy	CSA+MTX	PK	89	Var/-
10	Primary	MDS	PK	Cy+ATG	CSA+MTX	Flu	CSA+MTX	PK	30	Var/-
11	Primary	AA	Kİ	Cy+ATG	CSA+MTX	Flu	CSA+MTX	PK	26	Vars/-
12	Primary	FAA	PK	Cy	CSA	Cy+ATG+Flu	CSA	PK	30	Yok/+
13	Primary	FAA	Kİ	Flu+Cy+ATG	CSA+MTX	Flu+Cy+ATG	CSA+MTX	PK	69	Yok/+

AÜTF deneyimi

- o 1 hastada farklı verici(haplo)
- o 4 /13 engrafman sağlandı.
- o Ortanca nötrofil engrafman:14 gün
- o Ortanca plt engrafman:18 gün
- o PGF ile sağkalım 53 ay,SGF ile 13 ay

Engraftman yetmezliđi?

Zayıf graft fonksiyonu?

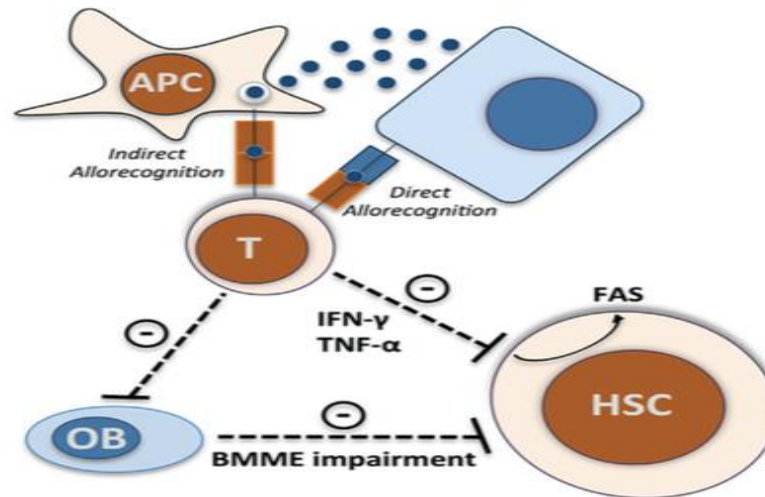
		Donör engrafman	Hematolojik toparlanma	Sitopeni	Relaps	Kemik iliđi	Kimeriz m
Engrafman yetmezliđi	Primer	Hayır	Hayır	Evet	Hayır	Hiposelüler	Miks veya full alıcı
	Sekonder	Evet	Evet				
Zayıf graft fonksiyonu	Primer	Evet	Hayır	Evet	Hayır	Hiposelüler	Full donör
	Sekonder	Evet	Evet				

Zayıf graft fonksiyonu tanım?

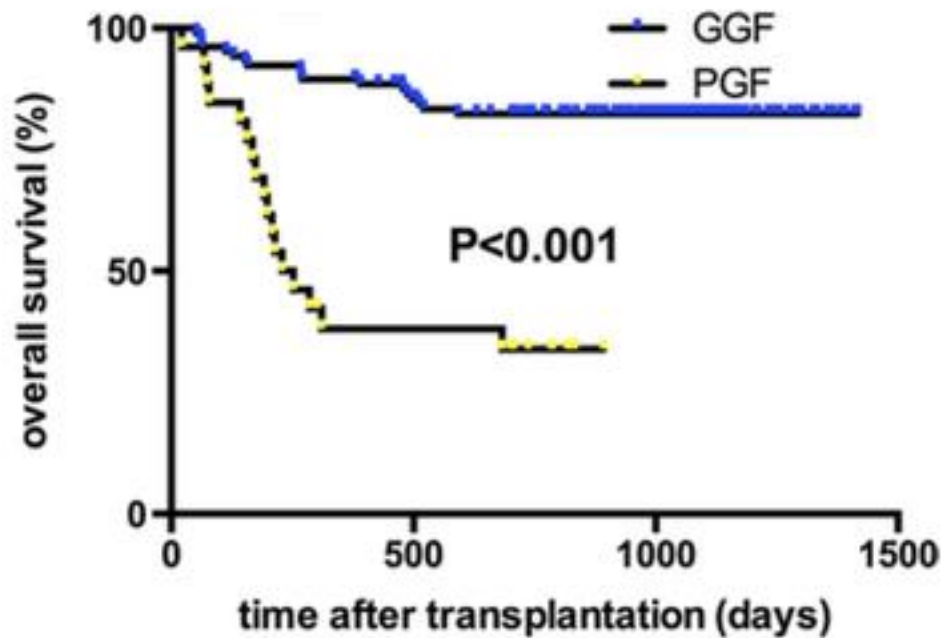
- 2 seride sitopeni ($\text{nötrofil} \leq 1.5 \times 10^9/\text{L}$, $\text{plt} \leq 30 \times 10^9/\text{L}$, $\text{Hb} \leq 8.5 \text{ g/dL}$) +14.günden sonra en az 2 hafta sürmeli,full donör kimerizm olmalı, relaps, GVHD, CMV olmamalı
- Persistan nötropeni ($\leq 0.5 \times 10^9 \text{ L}^{-1}$), $\text{plt} \leq 20 \times 10^9 \text{ L}^{-1}$), ve/veyahemoglobin $\leq 70 \text{ g L}^{-1}$ (28.gün itibari ile en az 3 gündür olmalı),full donör kimerik olmalı,relaps veya GVHD olmamalı



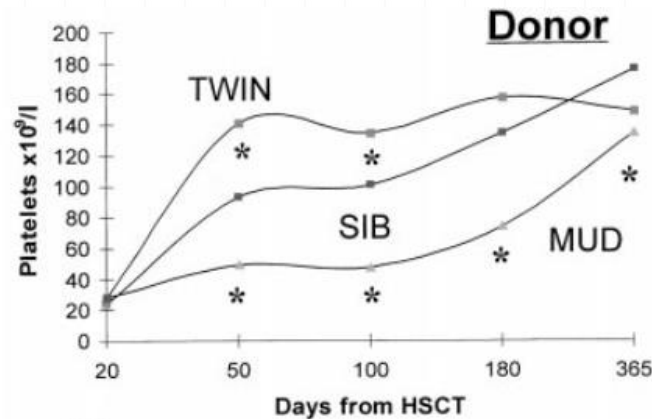
Zayıf graft fonksiyonu -patogenez-



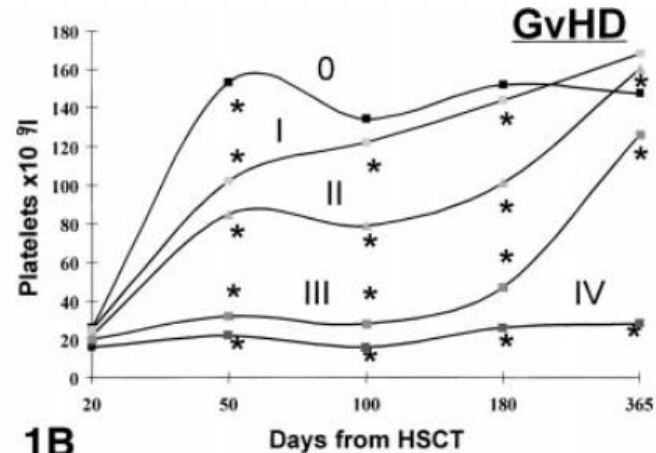
Zayıf graft fonksiyonu



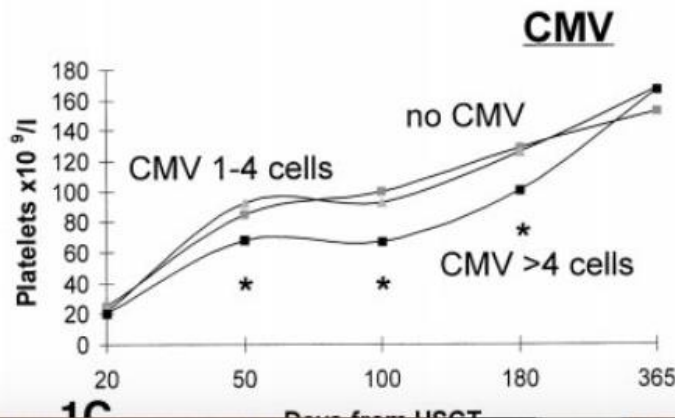
Zayıf graft fonksiyonu



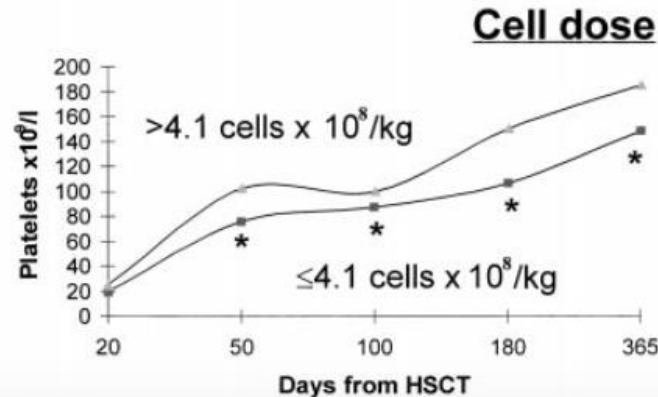
1A



1B



1C



1D

Dominietto A, Br j hematol 2001

Zayıf graft fonksiyonu

- Yaş,ABO uyumsuzluğu,CMV infeksiyon ZGF'de önemlidir.

Xiao Y,Int j med sciences 2015

- Haploidentik nakillerde yaş,cinsiyet,tanı,ABO uyumsuzluğu ve hücre dozundan bağımsız olarak ZGF artar.

Sun Y,Ann Hematol 2015

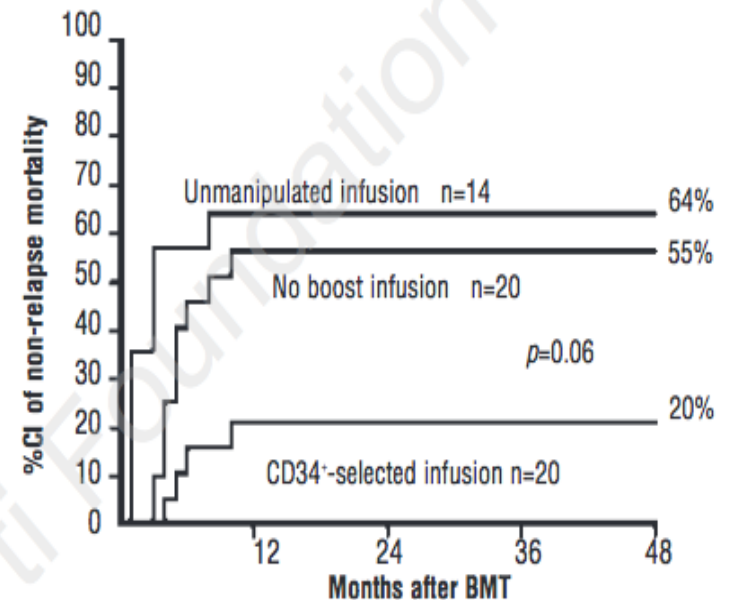
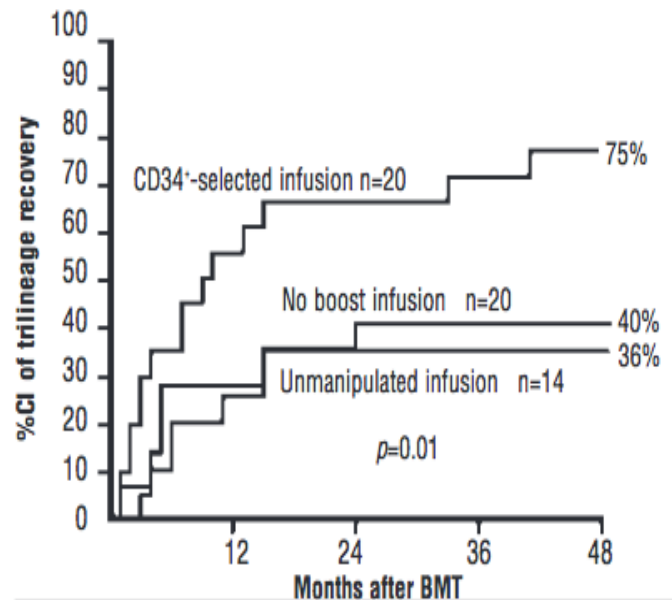
- Myelofibrozis; yaş,>10 cm dalak ZGF için anlamlı iken, fibrozis derecesi anlamlı bulunmamış.

Alchaby A,BMT 2016

Zayıf graft fonksiyonu

-Hazırlık rejimi verilmeden

CD34+hücre infüzyonu-



Zayıf graft fonksiyonu -Hazırlık rejimi verilmeden CD34+hücre hücre infüzyonu-

	Klyuchnikov et al. (2013) ^a	Askaa et al. (2014)	Stasia et al. (2014)	This study	Total or average
# of patients	32	18	41	20	111
MRD	11 (34 %)	6 (33 %)	12 (29 %)	0 (0 %)	29/111 (26 %)
MMRD	0 (0 %)	0 (0 %)	11 (27 %)	0 (0 %)	11/111 (10 %)
MUD	15 (47 %)	10 (57 %)	18 (34 %)	8 (40 %)	51/111 (46 %)
MMUD	6 (19 %)	2 (11 %)	0 (0 %)	11 (55 %)	19/111 (15 %)
HRD	0 (0 %)	0 (0 %)	0 (0 %)	1 (5 %)	1/111 (1 %)
CD34 ⁺ cells in SCB ($\times 10^6$ /kg)	3.4	4.9	3.5	4.6	4.5
CD3 ⁺ cells in SCB ($\times 10^4$ /kg)	0.9	1.1	0.6	0.2	0.7
Hematologic recovery	81 %	72 %	75 %	92 %	80 %
aGvHD grades II–IV	6 (19 %)	2 (11 %)	9 (22 %)	1 (5 %)	20 (18 %)
aGvHD grades III–IV	4 (13 %)	2 (11 %)	0 (0 %)	0 (0 %)	6/111 (5 %)
Median FU (days)	900	1072	1245	961	1045
3-Year OS	45 %	40 %	63 %	53 %	50 %

SONUÇ OLARAK..

- Engrafman yetmezliği ile zayıf graft fonksiyonu tanımı/patogenezi farklıdır.
- Engrafman yetmezliğinden korunmak için iyi donör seçilmeli,intensifiye hazırlık rejimleri tercih edilmeli, verilen kök hücre dozuna dikkat edilmelidir.
- Anti HLA antikorlarının nakil öncesinde azaltılması engrafman yetmezliği riskini azaltabilir.
- 2.nakil veya Hazırlık rejimi olmaksızın CD34+ hücre infüzyonu tedavide kullanılabilir.