Acquired Aplastic Anemia : The Ideal Conditioning Regimen

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Special Considerations when Planning HSCT for Bone Marrow Failure Disorders

AIM : RESTORE ACTIVE HEMATOPOIESIS

No Malignancy to Eradicate with GvL	**NO BENEFIT OF GVHD / No GvL**
Myeloablation not required (Aplastic)	**USE RIC REGIMEN**
Need to Secure Engraftment	**MAXIMAL LYMPHO-/IMMUNO ABLATION**
Young Patients	**FERTILITY PRESERVATION**

Actuarial probability of graft failure in AA patients according to number of pretransplant transfusions

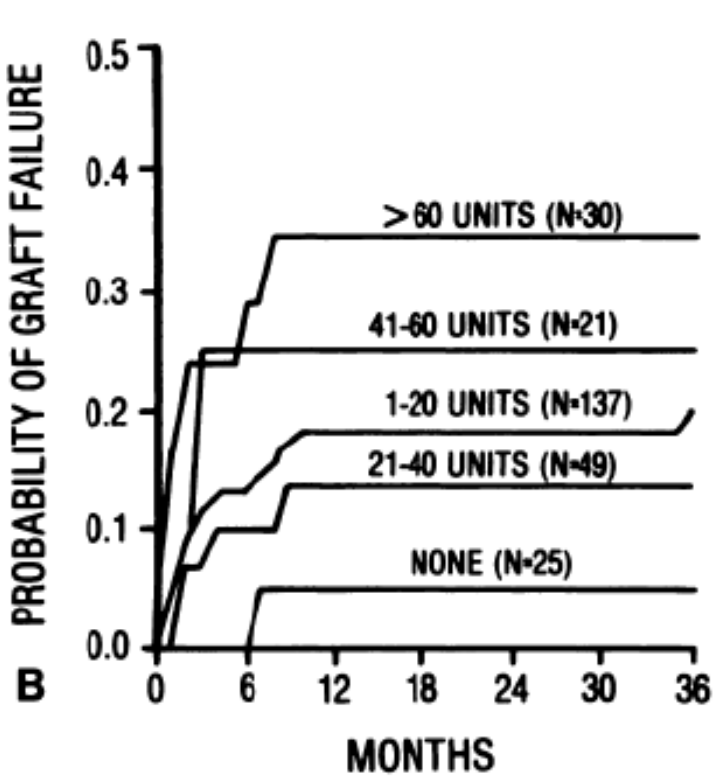


Fig 2. Actuarial probability of graft failure in patients receiving cyclophosphamide alone for pretransplant conditioning according to (A) whether corticosteroids were used to treat aplastic anemia prior to transplantation and (B) number of pretransplant transfusions.

Period: 1978-1986

Champlin et al., Blood 73: 606-613 (1989)

- Matched Sibling HSCT
- Matched Unrelated Donor HSCT
- Cord Blood Transplantation

Matched Sibling Donor HSCT for Aplastic Anemia

Cyclophosphamide only conditioning (CY only)

Cyclophosphamide and ATG (CY/ATG)

Fludarabine based (FLU/CY)+/-ATG

Alemtuzumab based conditioning

Elderly patients

Cyclophosphamide Only Conditioning

CY is considered the traditional backbone for conditioning of bone marrow failure

CIBMTR prospective randomized study

CY50 mg/kg D-5 to D-2

Add Horse ATG 30 mg/kg D-5 to D-3

5 years probability of survival is 74% for CY and 80% for CY/ATG (P=0.44)

GF, GVHD, similar on both groups

The study was not adequately powered to detect significant differences between the two groups

Champlin RE, et al. Blood 2007; 109:4582-4585.

Antithymocyte Globulin (ATG) Based Conditioning - I

ATG based conditioning :

- First explored in Boston and Seattle group
- In context of transplants in patients with graft failure but later on applied to first transplants

Subsequent studies:

- CY/ATG combination for upfront HSCT : excellent engraftment rate, (>90%)
- relatively low incidence of both aGVHD and cGVHD with
- Excellent long term overall survival (80-90% at 10 years)

Smith BR, et al. Transplantation. 1985;39:671-673
Storb R, et al. Blood. 1976;48:817-841
Storb R, et al. Blood. 1994;84:941-949
Kahl C, et al.. Br J Haematol. 2005;130:747-751

ATG Preparations

Commercial Name	Manufacturer	Source	Current Status
Lymphoglobulin	Genzyme	Horse	Discontinued
ATGAM	Pharmacia/UpJohn Now Pfizer	Horse	Commercially available Not available in Europe
Thymoglobulin	Sanofi	Rabbit	Available
ATG-Fersenius	Fersenius	Rabbit	Available

ATG Preparations

- Rabbit and equine ATG have different pharmacokinetics profile:
  - Rabbit ATG (rATG): 29.8 days
  - Horse ATG (hATG): 5.7 days
- Consequently :
  - rATG can deplete transplanted donor T cells in vivo much more efficiently as opposed to hATG
  - Can prevent acute GVHD but at the expense of possibly higher incidence of graft rejection and delayed immune reconstitution.

Bunn D et al. Clin Nephrol. 1996; 45(1):29–32
Vo PT, Pantin J, Hematol Oncol. 2015; 26;8:78

Alemtuzumab Conditioning Regimens

- Alemtuzumab (CAMPATH) monoclonal Ab against CD52
- CD52, a GPI-linked membrane protein expressed on almost all WBC but not on CD34 HSC
- Potent lympholytic agent
- Detected in the plasma for several weeks after administration resulting in depletion of recipient auto reactive lymphocytes
  - Prevents GVHD by depletion of donor allo-reactive T-cells

Gandhi S,et al. Int J Hematol. 2013 May;97(5):573-80

Alemtuzumab (CAMPATH-IG) Conditioning Regimens

- Use of Alemtuzumab was consistently associated with high incidence of mixed chimerism which tips the balance away from GVHD

- High survival of early patients with graft failure was in part due to a high incidence of autologous recovery

Gandhi S,et al. Int J Hematol. 2013 May;97(5):573-80

Alemtuzumab Conditioning Regimens

- Significant proportion (20-40%) of patients with AA have an associated PNH clone with defective expression of CD52 on T-cells.

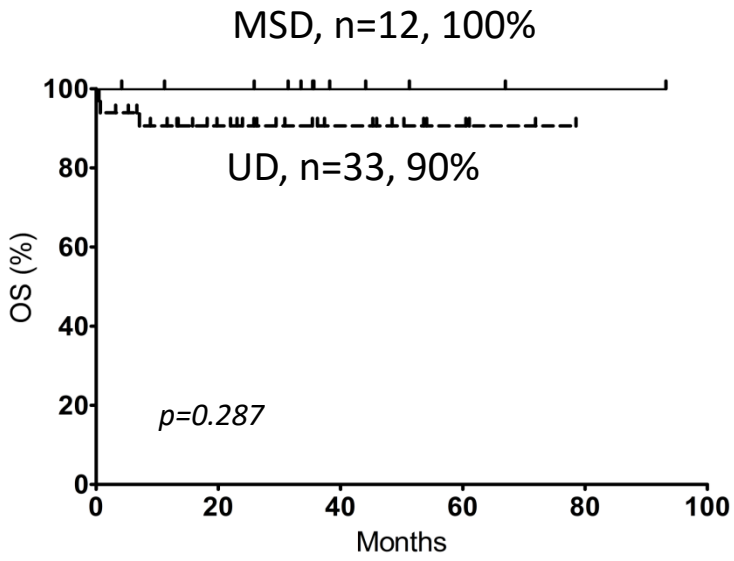
- In these patients ATG is considered as an alternative

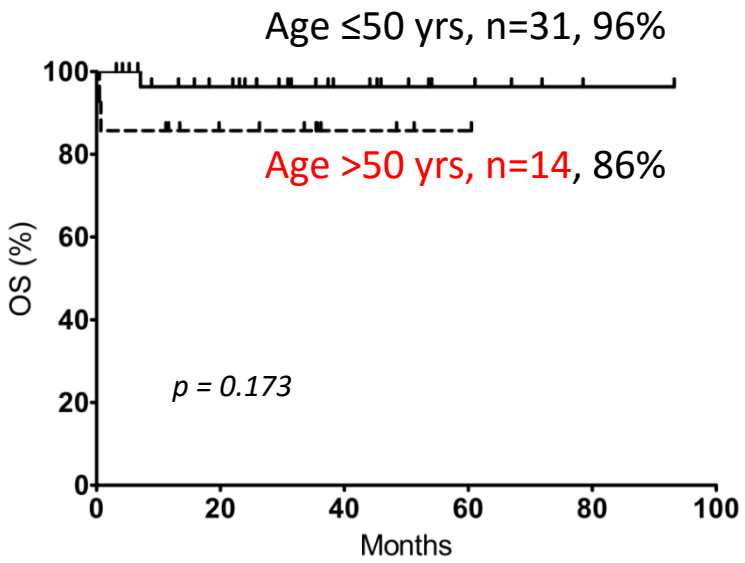
Gandhi S,et al. Int J Hematol. 2013 May;97(5):573-80

King's FCC conditioning for idiopathic SAA

- FLU 30mg/m2 x 4
- CY 300mg/m2 x 4
- Alemtuzumab (Campath-1H) 0.2mg/kg x 5
- Post graft ciclosporin (no methotrexate needed)
- For MUD HSCT, no irradiation needed

N = 45, transplanted 2007-2015

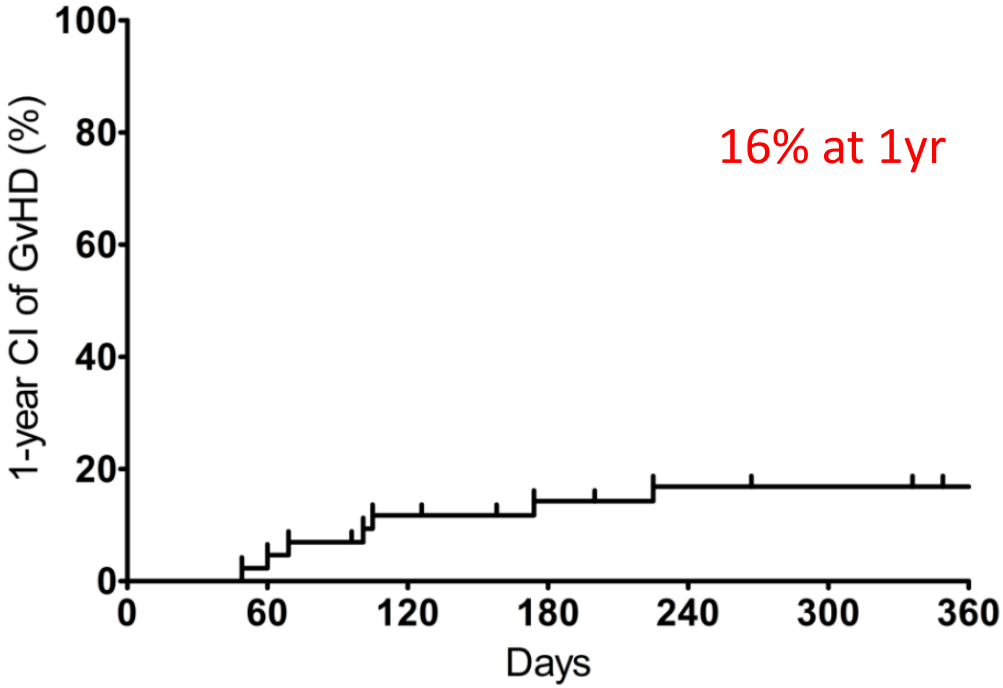




Grimaldi et al, unpublished data 2016

FCC HSCT - Patient outcomes

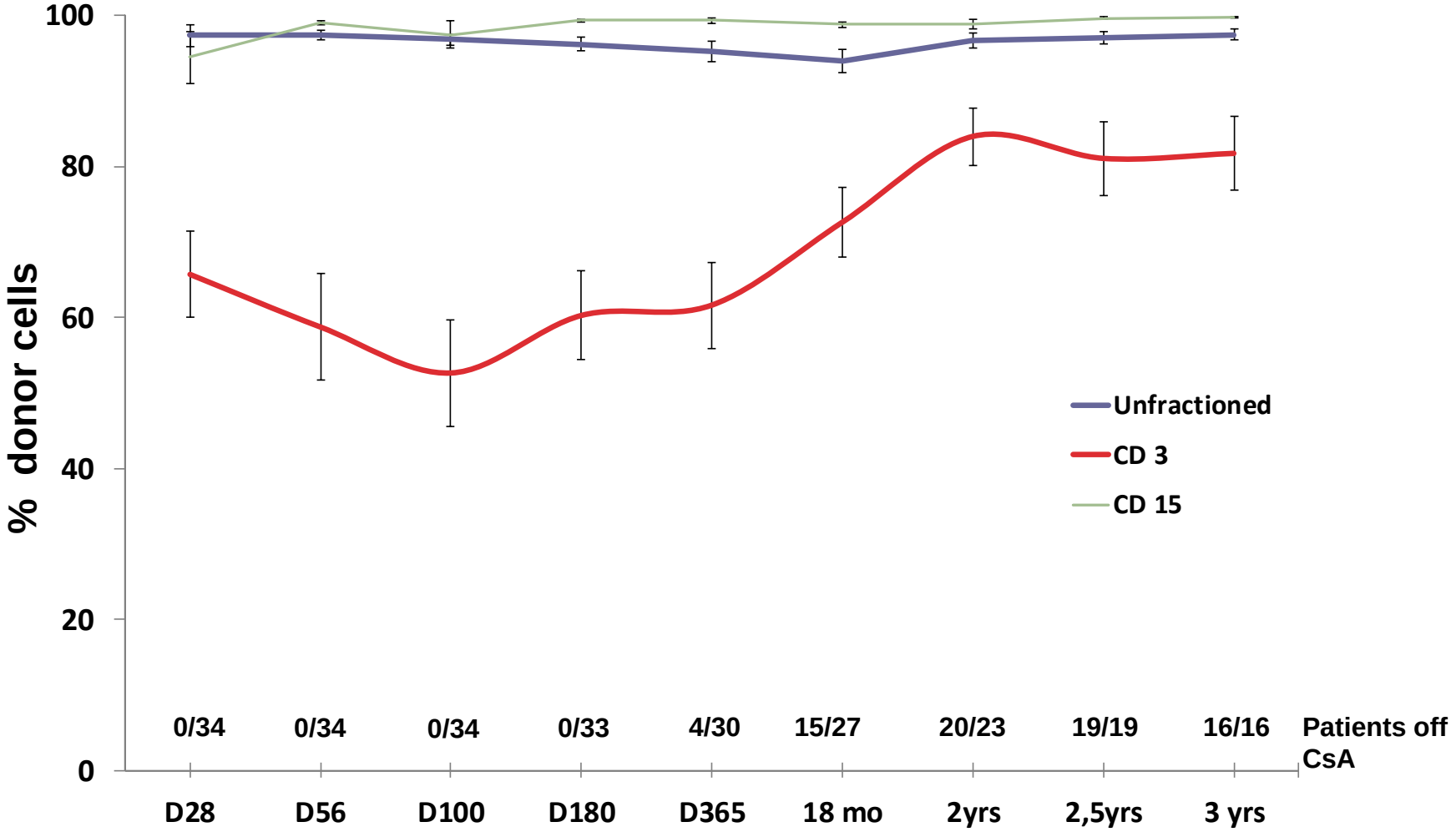
N=	45
Median days to ANC > $0.5x10^9$/l	12 (10-22)
Median days to platelets > $20x10^9$/l	12 (9-61)
Graft failure (primary)	1 (2.3%)
1 year TRM	3 (6.6%)
Acute GVHD	6 (13.6%) - 5/6 grade I/II, skin only
Chronic GVHD Mild/Moderate/ Severe	6 (13.3%) 4/1/1



Cumulative incidence of GVHD (acute + chronic)

Grimaldi et al, unpublished data 2016

Persistent mixed T-cell chimerism despite CsA discontinuation



Grimaldi et al, unpublished data 2016

Studies on CAMPATH based regimen conditioning for SAA patients

Study	Design	No.	Age	Donor type, n (%)	Conditioning	OS	EFS	aGVHD	cGVHD	infections	Graft failure
MARSH et al, 2011	retrospective multicenter study	50	35 (8-62)	MSD N= 21 (42%) MUD n= 29 (58%)	fludarabine 30 mg/m2 IV/dcX4 CY 300 mg/m2 IV /d X4 Alemtuzumab 40-100 mg/d iv or s.c x4	88% @2 yrs	80 % @2 yrs	N= 7 (13.7%)	N= 2 (4%)	EBV 4(8%) CMV 9(19%) ADENOVIRUS 7 (15%)	N= 6 (12%),
Samarasinghe et al, 2012	multicentre retrospective study	43	11 (0·5–17)	MUD	Flu 30 mg/m2 x 5 Cy 120-200 mg/kg X 2-4 d Campath (0·9–1 mg/kg)	95% @5 yrs	NA	2·3%	2·3%	CMV (22·7%)	0
Hamad et al 2014	retrospective study	41	37 (17-59)	MSD MUD MMRD	Cy 22% Cy/flu 71% Flu/BU 2% Flu/ Bu /TB 4% GVHD prophylaxis CAMPATH/ CSA 37 (90) CAMPATH/ tacrolimus 3 (7) CAMPATH/ MMF 1 (2) CAMPATH dose 60 mg 35 (85) 50 mg 6 (15)	85 % @3 yrs	N/A	NONE >G1	1/33 (3%)	Bacterial sepsis 21 (51%) CMV 19/25 (79%)	4 (10%)
Gupta et al.2004	retrospective study	33	16 (4-45)	N/A	CY 50 mg/kg x 4 0.75 -1 mg/kg x 4-8 d	81% @5 yrs		4 (13%)	0 (0%)	15 (45%)	8/33 (24%)
Novitzky et al, 2013	Prospective study	30	19 (7-60)	MSD	fludarabine 30 mg/m2 x 5 days cy 60 mg/kg x 2 days Campath "in the bag"	100% @1 yr	96% @1 yr	0	0	7 (23)	2/30
Kanda et.al. 2013	retrospective study	15	34 (20–46)	MUD	Fludarabine 30 mg/kg x 4 CY 25 mg/kg x 4 Campath 0.16 mg/kg/day x 6 TBI 2 Gy	83.3 % @1 yr	NA	0	0	NA	8.3 %
Siegal et al 2008	retrospective study	10	40 (25–56)	MRD 8 (80) Alternative donor (MMFD, MUD) 2 (20)	High-dose CY based 3 (30) Fludarabine based 7 (70)	7/10 (70) @1 yr	7/10 (70) @1 yr	1/9 (11%)	0	Bacterial 6/10 (60) Fungal 2/10 (20) Viral CMVreactivation 5/6 (83) H.Z 2/10 (20)	1/10 (10%)
Gupta et al, 2005	retrospective study	7	13 (8-35)	MUD	Alemtuzumab 0.2 mg/kg/day x 5 Flu 30 mg/m2 x 5 CY 20 mg/kg x 4	6/7 @10 mo	6/6 @6mos	3/7	1/6	CMV 1/6	0

Radiation-based Conditioning Regimens for MSD HSCT

- Lower rates of graft failure, at the expense of :
  - Significant early toxicities like GVHD and pneumonitis
  - Late toxicity including:
    - Secondary malignancies and
    - Reduced growth and development in children

Justified in alternate donor or allo-immunized

Sanders JE, et al. Blood. 2011;18:1421–8
Champlin RE, et al. Blood. 1989; 73:606-613
Gluckman E, et al. Blood. 1992;79:269-275
Deeg HJ, et al. Blood. 1996;87:386-392

Fludarabine based conditioning

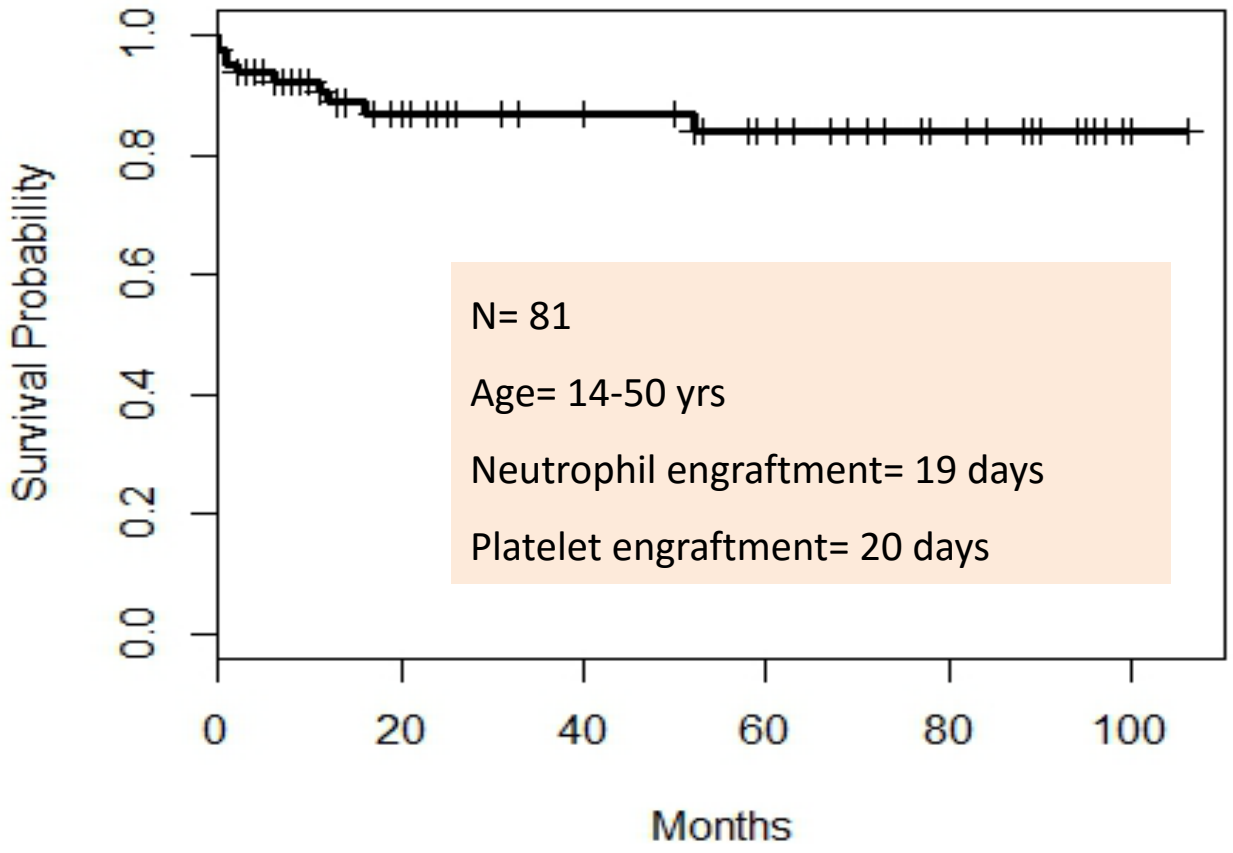
FLU/CY

- **increasingly used in situations where ATG is not available or cannot be used**
- **Extremely low toxicity and low risk of graft failure**
- **Possible increase in GVHD risk remains an important concern**

Maury S, et al. Haematologica 2009; 94:1312-1315
AL-Zahrani H,et al .BBMT 2011; 17: 717-722

Study	Design	Number	Age	Donor type	Conditioning	OS	EFS	aGVHD	cGVHD	Graft failure
Bacigalupo et al, 2005	Retrospective multicenter	38	14 (3-37)	MMRD n=5 MUD n=33	Flu/Cy/ ATG	29/38	92% at 1 year	2/35	2/35	7/38
Bacigalupo et al, 2010	Retrospective	100	13 (3=51) 27(7-53)	Alternate donor	Flu/Cy/ ATG n=52 Flu/Cy/ATG/TBI n=48	73% 79%	-	18% 7%	1/52 4/48	17% 17%
Maury et al, 2009	Prospective	30	46 (31-66) 39(30-67)	MSD	Flu/Cy±ATG n=30 Cy±ATG n=239	77% 60% at 5 years	-	3 (10%) 46 (19%)	3(13% 21 (13%)	0% 11% 1ry GF
Alzahrani et al, 2011	Retrospective	38	20(14-36)	MSD	Flu/Cy	79% at 43 months	-	4 (11%)	8(25%)	1(3%) at 43 months
George et al, 2007	Retrospective	35	20.8(5-43)	MSD	Flu/Cy±ATG	29/35 (82.8%)	29/35 (82.8%)	9/31(29%)	8/25(32%)	3/35(8.5%)
Go´mez-Almaguer et al.2006	Retrospective	23	25(4-65)	MSD	Flu/Cy±Bu	88% at 1500 days	-	0	0	8.7% at 1500 days
Xue et al. 2015	Prospective	20	7.5 (3-14)	MSD n= 13 MUD n=7	Flu/Cy/ ATG	19/20	18/20	0	0	1/20
Kang et al, 2014	Prospective	28	13.5(1-30)	MUD	Flu/Cy/ ATG	67.9%	-	13/28	2/25	0
Kudo et al, 2015	Retrospective	55	9 (1-15)	MSD MMRD MUD CB	Flu/Cy± ATG± TBI	45/55 (82.9%) at 4 years	81.2%	12/55	7/55	9/55
Mahmoud et al, 2015	Retrospective	273	19.7(1.5-51)	MSD	Flu/Cy n=181 Cy/ATG n= 92	74% at 8 years	-	42/273 (15%)	70/248 (28%)	3/273

KFSHRC FLU/CY Experience : Overall Survival

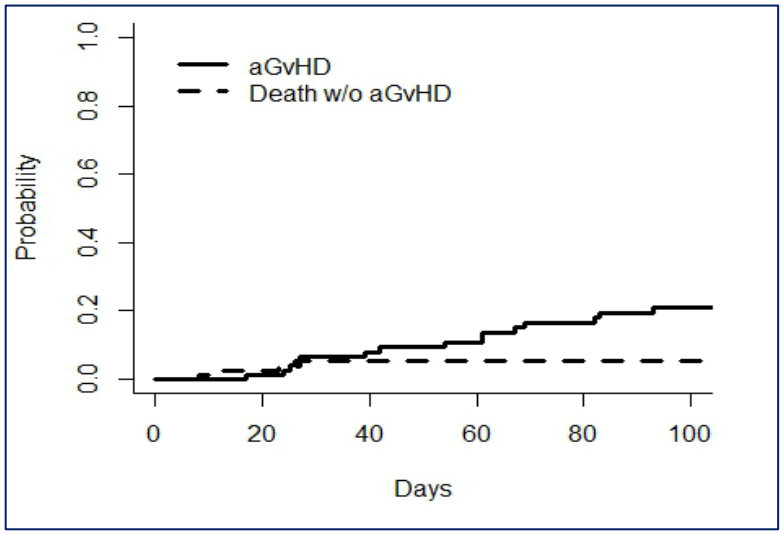


OS at 5-years= 80%

Shaheen M, et al . Unpublished data, 2016

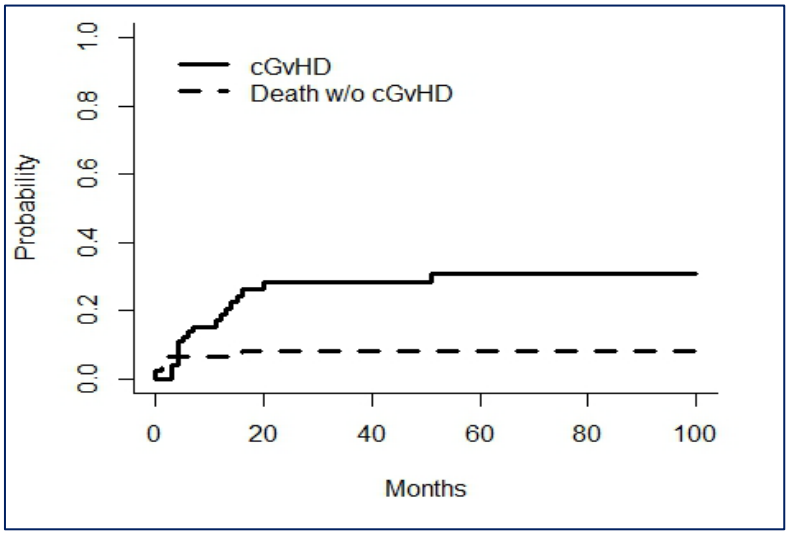
KFSHRC FLU/CY Experience

Acute GvHD(≥grade II)



Cumulative Incidence
aGvHD(≥grade II) = 20.9%
Death w/o aGvHD= 5%

Chronic GvHD



Cumulative Incidence:
cGvHD= 31%
Death w/o cGvHD= 8%

Shaheen M, et al . Unpublished data, 2016

Elder patients with SAA

Seminars in Hematology 2000; 37: 69

Age PMN	10 yy	20 yy	30 yy	40 yy	50 yy
0	24	20	14	16	-2
100	19	14	8	1	-7
200	14	9	3	-4	-11
300	16	5	-1	-7	-14
400	6	1	-4	-10	-16
500	3	-2	-7	-12	-17

Positive values: BMT has superior (+) survival compared to IS

Negative values: BMT has inferior (-) survival compared to IS

conditioning MSD in older patients

- Standard CY/ATG
- Limited data on the advantage of including FLU in the conditioning in these patients
- May receive a reduced intensity conditioning regimen using FLU/CY alone or more optimally Flu/CY with adjusted doses of ATG or Alemtuzumab (FCC)

Maury S, et al. Haematologica 2009; 94:1312-1315
AL-Zahrani H,et al .BBMT 2011; 17: 717-722

Conditioning for MUD HSCT

- MUD second line treatment and possibly upfront treatment for young patients with very severe aplasia.

- Induction of engraftment against immune barriers

- Standard CY/ATG did not provide sufficient immuno and lympho ablation for sustained engraftment in MUD HSCT
- Addition of TBI to CY/ATG in MUD **:** Best survival was achieved with a TBI dose of 200 rads

Bacigalupo A, et al.Haematologica. 2010;95(6):976-82
Deeg HJ, et al. Blood. 2006 ;108(5):1485-91

Conditioning for MUD HSCT

- Having established the optimal dose of TBI of 200 rads, a North American study looked at the optimal dose of Cyclophosphamide with fixed doses of ATG, Fludarabine and TBI 200.
- CY 0, 50, 100, 150 mg/kg were tested
- CY 0 closed after 3 graft failures
- CY 150 closed due to excess toxicity
- Leaving CY 50-150 as the possible dose choice
- More recent study, CY 50 vs CY 100 in combination with fixed doses of ATG, Fludarabine and TBI 200

	Cyclophosphamide 50 mg/kg (n=38)	Cyclophosphamide 100 mg/kg (n=41)
Graft failure, primary and secondary	3 (8%)	6(15%)
Survival	37 (97%)	39 (95%)
Major regimen-related toxicity* (grade 3 or higher)	4 (11%)	9 (22%)
Alive and engrafted	35 (92%)	35 (85%)

Tolar J, et al. Biol Blood Marrow Transplant. 2012 18(7):1007-11
Anderlini P, et al. Lancet Haematol. 2015; 2(9); 367-375

Conditioning for MUD HSCT

1. CY is important component of conditioning, 50-100 mg (data support 50)
2. TBI helps to promote engraftment and prevent rejection, but should be limited to 200 rads
3. Cy> 100 should not be used in combination with TBI
4. Fludarabine and ATG help in promoting engraftment and preventing rejection
5. The combination of CY 50/TBI 200/Flu/ATG is the most optimal conditioning at present
6. FCC is a strong emerging radiation free alternative with encouraging results.

CBT for Acquired Aplastic Anemia

1. Only few reports, poor outcome. Good outcome in related CBT
2. Possible option for patients who had failed ISP, no MUD with available CB units with adequate TNC
3. Large cohort of 31 Japanese patients, 2 years OS 41%.
4. Eurocord 71 patients (1996-2009)

   Median age 13 years, 28 adults (9 with PNH), RIC regimen was used on 68%, 3 years OS 38%

Yoshimi A, et al, BBMT 2008;
Peffault de Latour R , et al, BBMT 2011; 17: 78

Conditioning for Unrelated CBT
Ongoing French Society of SCT and Eurocord (APCORD-Protocol)
Prospective Phase II Study on Unrelated CBT

Fludarabine	30 mg/m^2	D-6 to D-3
Cyclophosphamide	30 mg/kg	D-6 to D-3
Thymoglobulin	2.5 mg/kg	D-3 to D-2
TBI	200 rads	D-2

3-55 years, failed ISP, no MUD, no clonal evolution, KPS > 60, one or two units CB with total $\geq$ TNC 4 x 10^7.

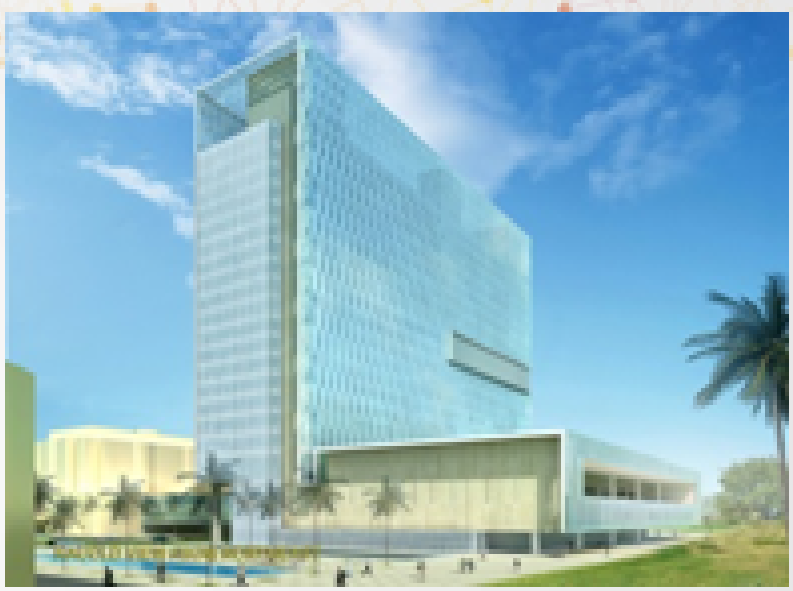
Result is still pending

Conditioning for Bone Marrow Failure of PNH

- PNH/AA patients transplanted for concomitant AA should follow the same conditioning regimens used for AA for related and MUD HSCT
- Some investigators suggested that a “graft versus PNH” effect may be needed to eradicate the PNH clone, especially in non-hypoplastic PNH
- No specific guidelines are available for patients transplanted for thrombosis or hemolytic indications,
- Myeloablative conditioning have been used in non-hypoplastic PNH (even Busulfan-based)

Takahashi Y, et al. Blood. 2004;103:1383-1390
Raiola AM, et al. Haematologica. 2000;85:59-62

Acknowledgement



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