IPIG
International PNH Interest Group

Allogeneic stem cell transplantation for patients with PNH

Xiao-Jun Huang M.D.

National Clinical Research Center for Hematologic Disease

Peking University Institute of Hematology

Peking University People's Hospital

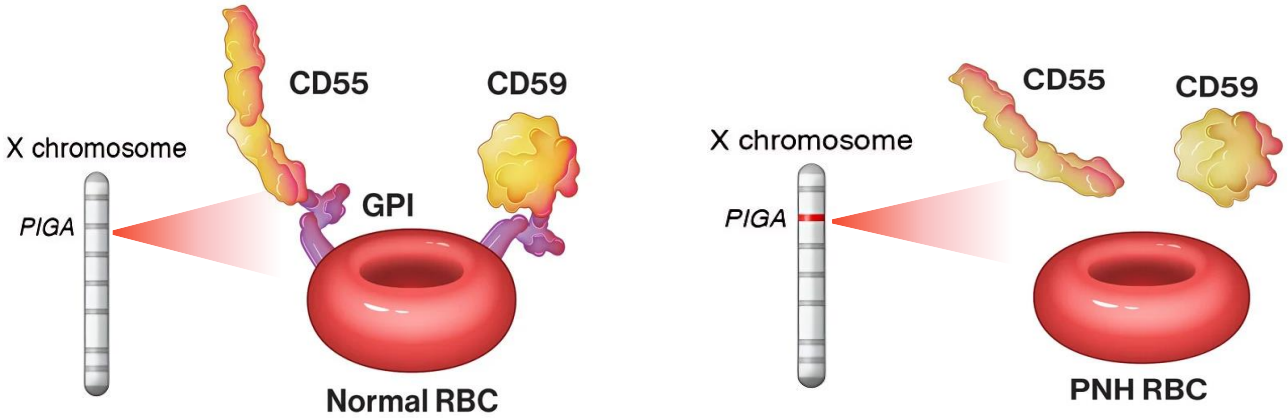
CONFLICT OF DISCLOSURES

I have no personal or financial interests to declare.

Content

Paroxysmal Nocturnal Hemoglobinuria (PNH)

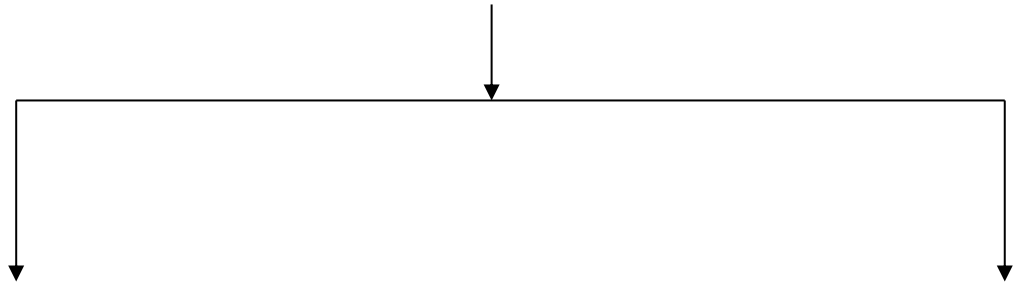
- PNH is a rare clonal HSC disorder caused by somatic mutation in the PIGA gene, leading to a deficiency of GPI-anchored proteins (complement regulatory protein CD55, CD59)
- The deficiency of CD55 and CD59 activates the complement system



- ✓ **Chronic hemolytic anemia** due to complement-mediated red cell lysis
- ✓ **Bone marrow failure** (BMF)
- ✓ **Thrombosis**

The treatment of PNH

The main strategy of PNH



Complement inhibitor

C5 inhibitor

C3 inhibitor

Factor B or D inhibitor

… …

Allo-HSCT

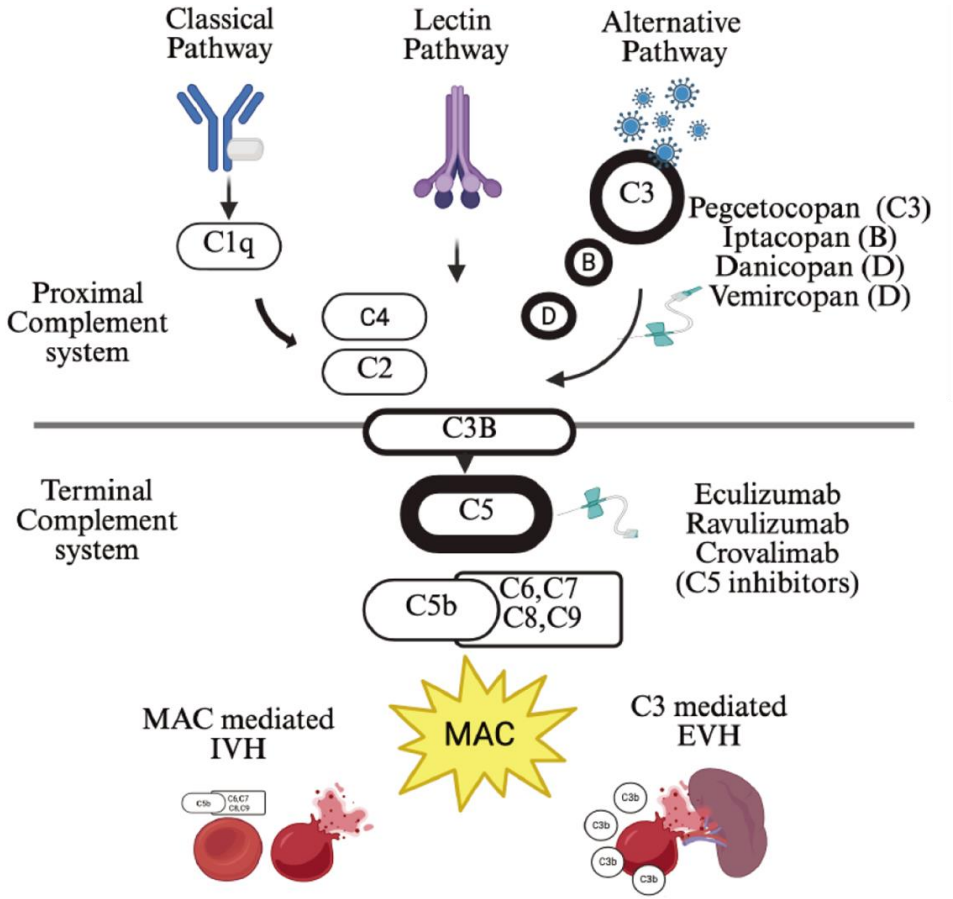
Matched sibling donor

Unrelated donor

Haploidentical donor

… …

The advancing landscape of novel complement inhibitors in PNH



FDA-approved complement inhibitors for PNH

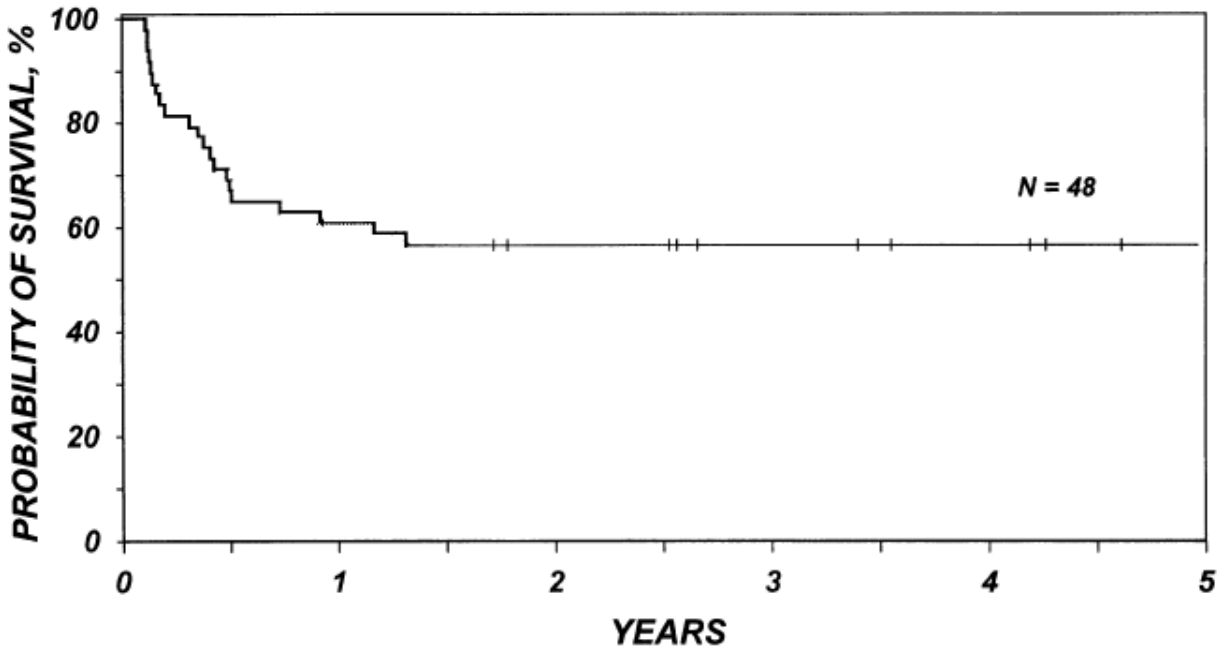
Drug (brand name)	Approval year	Mechanism of action	Route	Dosing frequency
Eculizumab (Soliris)	2007	C5 inhibitor	IV	Q2W
Ravulizumab (Ultomiris)	2018	C5 inhibitor	IV	Q8W
Pegcetacoplan (Empaveli)	2021	C3 inhibitor	SUBQ	BIW
Iptacopan (Fabhalta)	2023	Factor B inhibitor	Oral	BID
Danicopan (Voydeya)	2024	Factor D inhibitor	Oral	TID
Crovalimab (Piasky)	2024	C5 inhibitor	SUBQ	Q4W

MAC: membrane attack complex; **IVH:** intravascular hemolysis; **EVH:** extravascular hemolysis

The early outcomes of HSCT in PNH, mainly from MSD

Data from International Bone Marrow Transplant Registry (IBMTR) between 1978 and 1995

Age, median (range), years	28 (10–47)
Male sex, *n* (%)	26 (46%)
Severe aplastic anaemia pretransplant, *n* (%)	18 (32%)
Interval from diagnosis to transplant, median (range), months	26 (2–240)
Donor, *n* (%)	
HLA-identical sibling	48 (84%)
Identical twin	2 (3%)
Parent	1 (2%)
Unrelated donor	6 (11%)
Conditioning regimen (first transplant), *n* (%)	
Busulphan + cyclophosphamide	30 (53%)
Total body radiation + cyclophosphamide ± other	12 (21%)
Limited field radiation + cyclophosphamide ± other	11 (19%)
Cyclophosphamide alone	3 (5%)
None	1 (2%)



Survival after 48 HLA-identical sibling bone marrow transplants for PNH was 56%

The outcomes of HSCT in PNH from MSD or URD

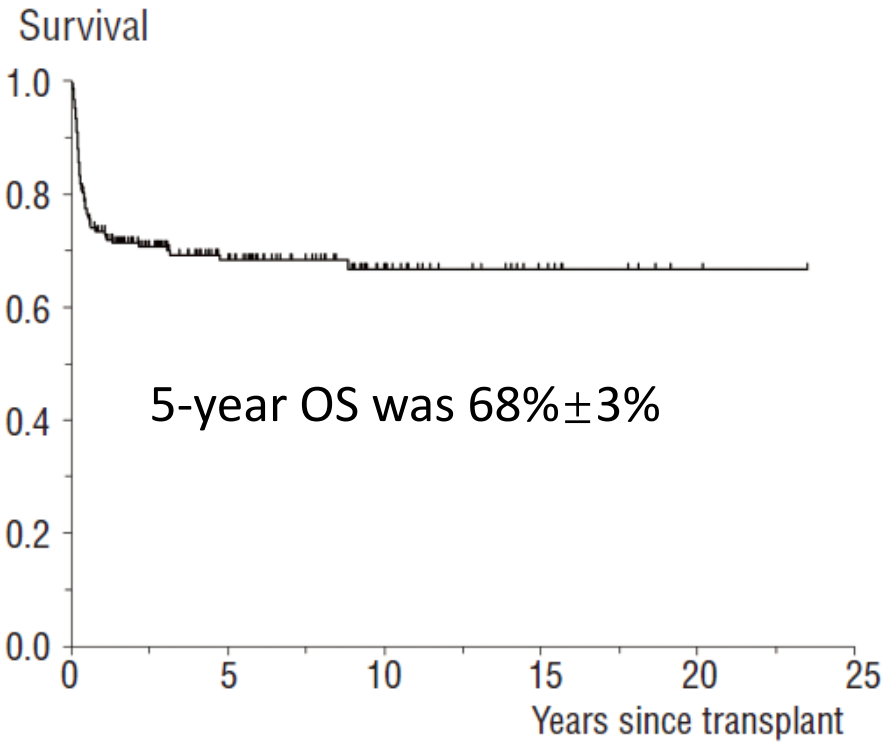
Data from EBMT between 1978 and 2007

Characteristics	n/N (%) or median (IQR$^{\phi}$), N
Gender, female	106/211 (50%)
Age at transplantation, years	30 (23-39)
Donor type	
HLA-identical sibling	136/210 (65%)
Source of stem cells$^{\alpha}$	
Bone marrow	135/210 (64%)
Peripheral blood stem cells	71/210 (34%)
Conditioning regimen	
Cyclophosphamide + busulfan	47/144 (33%)
Cyclophosphamide + total body irradiation (≥ 8 Gray)	22/144 (15%)
Cyclophosphamide + anti-thymocyte globulin	32/144(22%)
Fludarabine-based regimen	42/144 (29%)
GvHD prophylaxis	
Cyclosporine ± methotrexate	154/211 (73%)

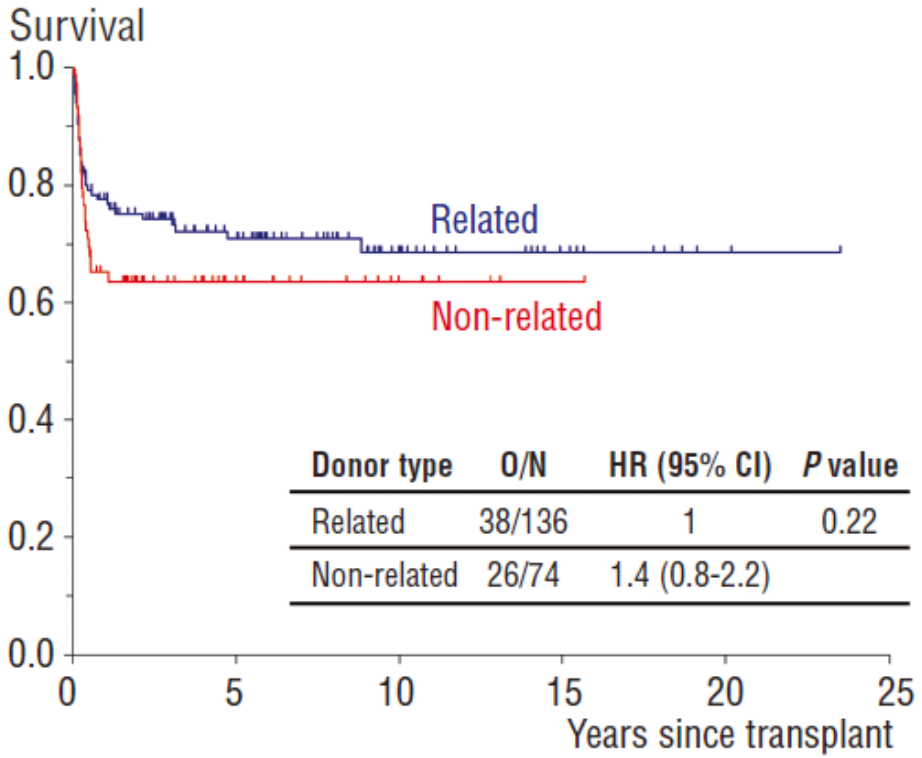
- 211 patients from 83 HSCT centers
- Median follow-up: 61months
- Engraftment failure: 7%
- Grade II-IV acute GvHD: 40%
- Chronic GvHD at 5 years: 29%
- Only 1 patient relapsed with PNH

The outcomes of HSCT in PNH from MSD or URD

Survival in the whole cohort

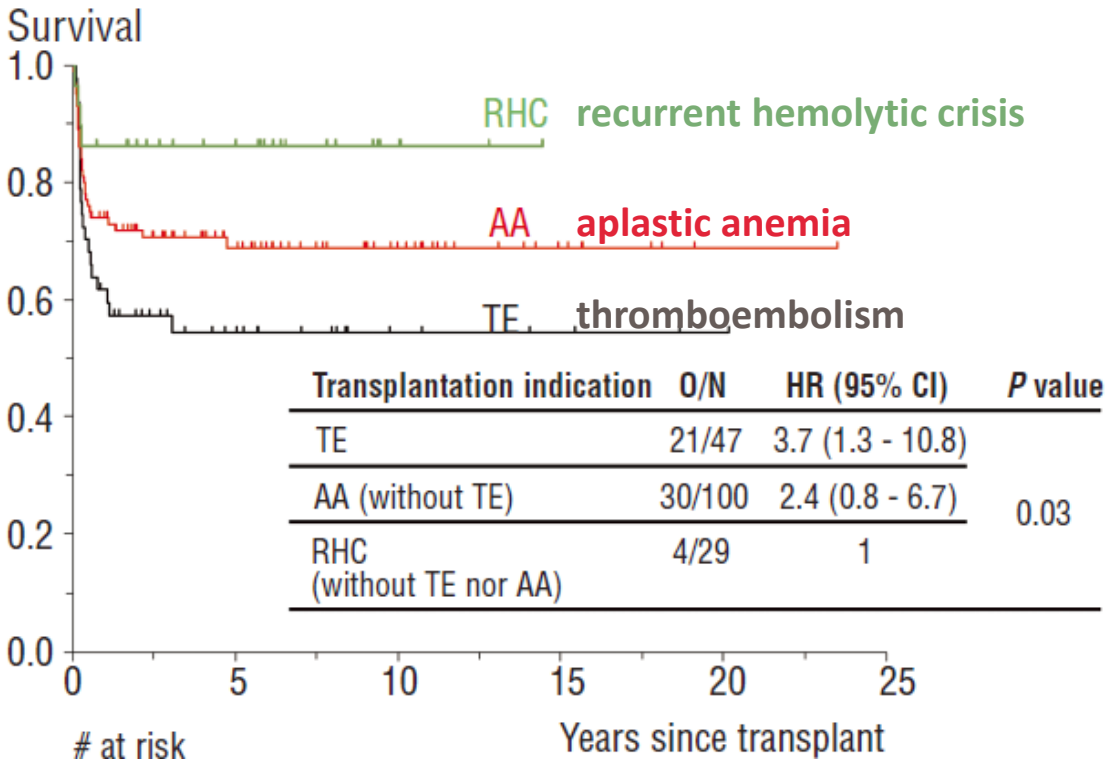


Survival according to donor type



Donor type	O/N	HR (95% CI)	*P* value
Related	38/136	1	0.22
Non-related	26/74	1.4 (0.8-2.2)	

The outcomes of HSCT in PNH based on transplant indication



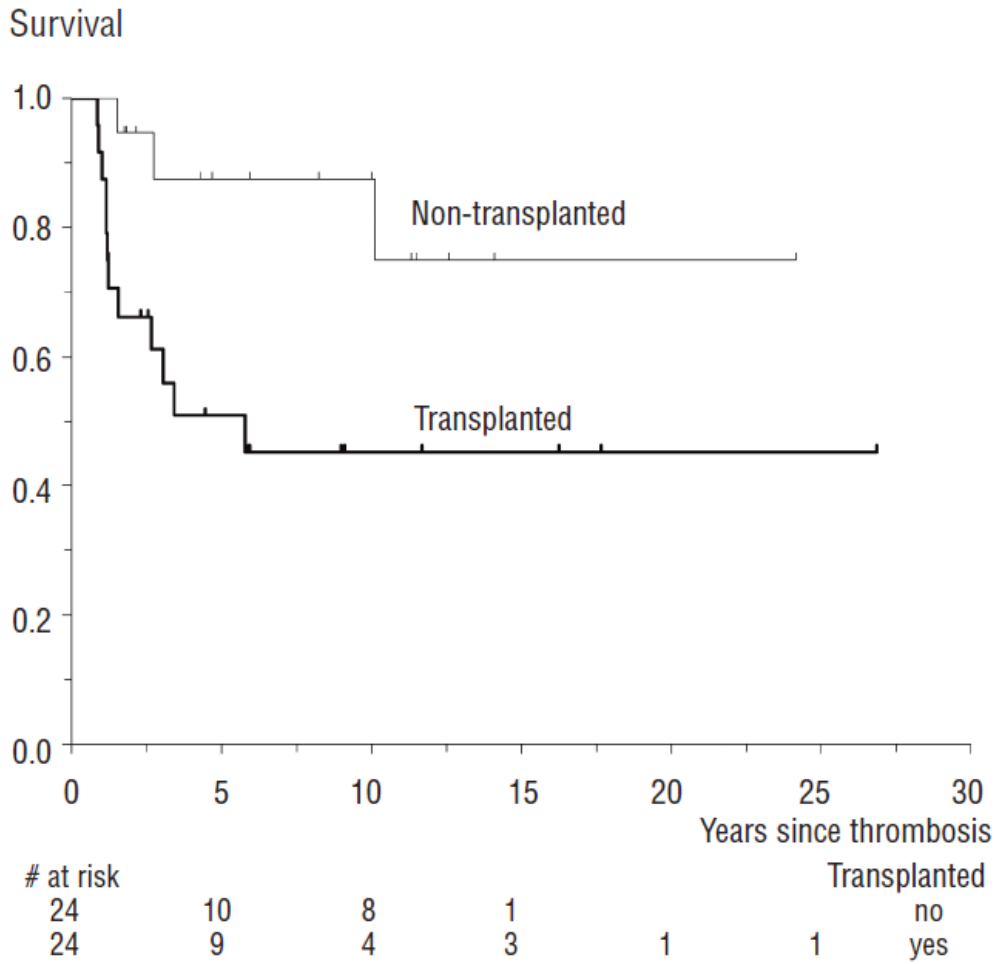
Transplantation indication	O/N	HR (95% CI)	*P* value
TE	21/47	3.7 (1.3 - 10.8)	0.03
AA (without TE)	30/100	2.4 (0.8 - 6.7)	
RHC (without TE nor AA)	4/29	1	

- The 5-year OS was 54%±7% in the case of thromboembolism (TE)
- The 5-year OS was 69%±5% in the case of aplastic anemia (AA) without TE
- The 5-year OS was 86%±6% in the case of recurrent hemolytic crisis (RHC) without TE or AA

Patients with thromboembolism failed to benefit from HSCT

Thrombosis: comparison of survival between transplanted and non-transplanted patients

- For the matched-pair analysis, 24 pairs of transplanted and non-transplanted patients have been identified.
- A significant difference was observed in OS between the two groups, with better OS for non-transplanted patients.



Updated Data from EBMT

240 PNH patients HSCT between 2011 and 2020 across 125 centers

Survival according to HSCT age

Patient age	Survival
<20 years	83%
20-40 years	82%
>40 years	67%

Survival according to Donor type

Donor type	Survival
Matched sibling	86%
Matched unrelated	78%
Mismatched unrelated	62%

The outcomes of HSCT in PNH with or without bone marrow failure (BMF)

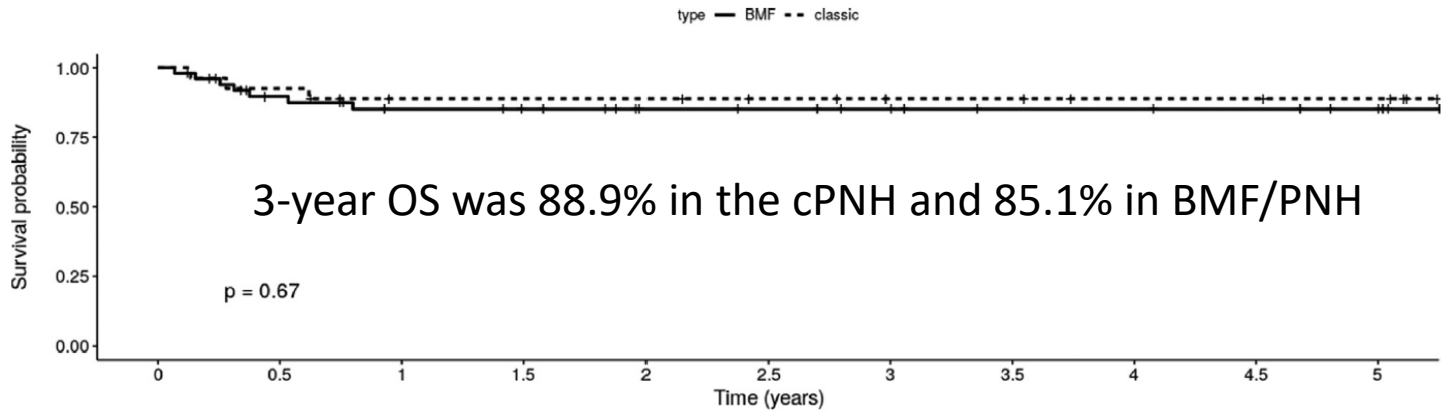
Data from Polish Acute Leukemia Group (PALG)

- **cPNH group**: a classical form of PNH, predominantly hemolytic without overt marrow failure.
- **BMF/PNH group**: a form associated with bone marrow failure (BMF), mostly aplastic anemia and incidentally myelodysplastic syndromes, irrespective of the presence or absence of hemolysis.

Characteristic	All Patients (N = 78)	cPNH Group (N = 27)	BMF/PNH Group (N = 51)	*P* Value
Age at allo-HSCT, yr, median (range)	29 (12-65)	35 (16-52)	27 (12-65)	.024
Time between diagnosis and allo-HSCT, mo, median (range)	12 (1-127)	20 (5-123)	9 (1-127)	.002
Clone size at allo-HSCT, %, median (range)	30 (0-95)	80 (0-95)	19 (.25-95)	.003
Number of patients tested	45	16	29	
Conditioning intensity, n (%)				.455
MAC	5 (6)	3 (11)	2 (4)	
RTC/RIC	73 (94)	24 (89)	49 (96)	
Donor, n (%)				1.0
Identical sibling	19 (24)	7 (26)	12 (23)	
MUD	49 (63)	16 (59)	33 (65)	
MMUD	10 (13)	4 (15)	6 (12)	

Similar outcomes of HSCT in PNH with or without bone marrow failure (BMF)

Characteristic	All Patients (N = 78)	cPNH Group (N = 27)	BMF/PNH Group (N = 51)	*P* Value
Engraftment, n (%)	75 (96)	26 (96)	49 (96)	1.0
Time to hematopoietic recovery, d, median (range)				
ANC >.5 × 10^9/L	18 (6-29)	19 (10-29)	18 (6-26)	.399
PLT >20 × 10^9/L	14 (5-35)	14 (11-27)	15 (5-35)	.421
Acute GVHD, all, n (%)	39 (50)	11 (41)	28 (55)	.341
Chronic GVHD, all, n (%)	22 (28)	9 (33)	13 (25)	.64
Chronic GVHD degree, n (%)				.086
Limited	14 (18)	8 (30)	6 (12)	
Extensive	7 (9)	1 (4)	6 (12)	
Missing data	1 (1)	0 (0)	1 (2)	
Donor chimerism				.528
%, median (range)	100 (86-100)	100(86-100)	100 (90-100)	



3-year OS was 88.9% in the cPNH and 85.1% in BMF/PNH

How we treat paroxysmal nocturnal hemoglobinuria

A consensus statement of the Canadian PNH Network

Recommendations

- We suggest that ASCT not be considered standard of care for patients with hemolytic PNH, **nor in patients with thromboembolism.**
- We suggest that ASCT be considered in patients with severe aplastic anemia and presence of a PNH clone, according to the same algorithms used for patients with severe aplastic anemia alone.
- We suggest that ASCT be considered in PNH patients with evidence of clonal evolution (eg, MDS, leukemia).

The indication of HSCT treating PNH from America or Europe

Candidates for HCT generally include those with life-threatening disease

- **Severe aplastic anemia who have an available HLA-matched donor**
- **PNH complications unresponsive to eculizumab orunavailable eculizumab**
- **Some high-risk MDS**

- Before the era of eculizumab, HSCT were performed in patients with severe hemolysis or thrombosis and young patients with severe AA who had an HLA-identical donor or did not respond to immunosuppressive therapy.
- Since the year of 2009, the number of HSCTs decreased dramatically, owing to the wide use of eculizumab in countries where eculizumab was available.

Summary I

- The main therapies of PNH comprise complement inhibitors and allo-HSCT
- Published multicenter data were mainly from matched sibling or unrelated donors
- Is haploidentical transplantation a viable option for PNH?

Content

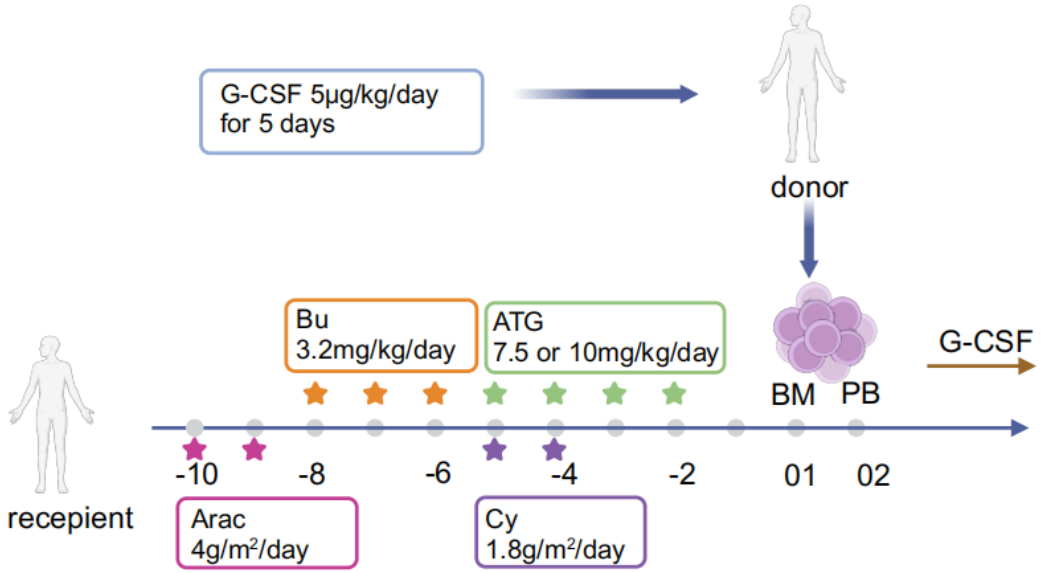
1 The evolution of HSCT in Paroxysmal Nocturnal Hemoglobinuria

2 **The development of G-CSF/ATG based haploidentical protocol**

3 Haploidentical HSCT for PNH

Two strategies in haplo-SCT for malignant hematoligical diseases

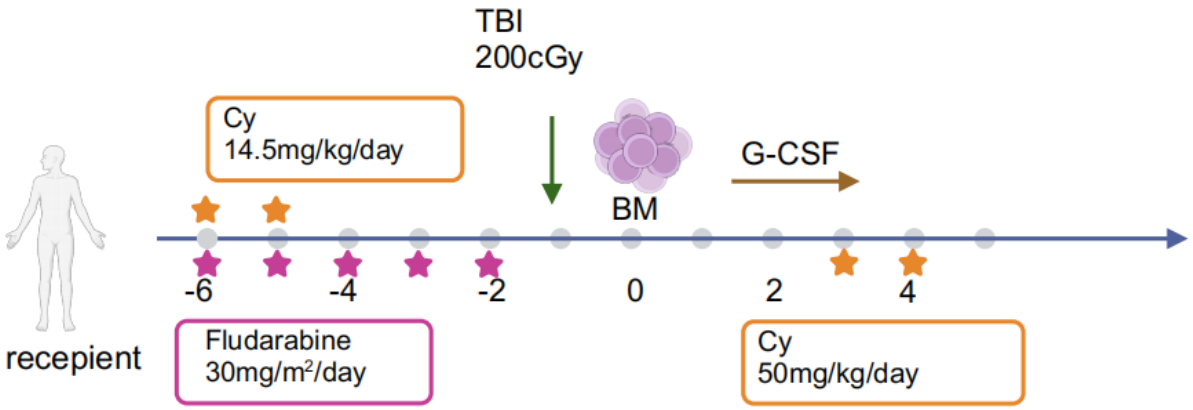
G-CSF/ATG based protocol



The first clinical report of G-CSF/ATG based protocol in 2004

Huang XJ, et al. Chin Med J (Engl). 2004

PT-Cy based protocol



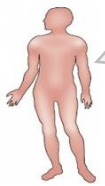
The first clinical report of PT-Cy based protocol in 2008

Luznik, et al. Biol Blood Marrow Transplant. 2008.

Novel regimen in haplo-SCT for leukemia

Novel regimen for immune tolerance

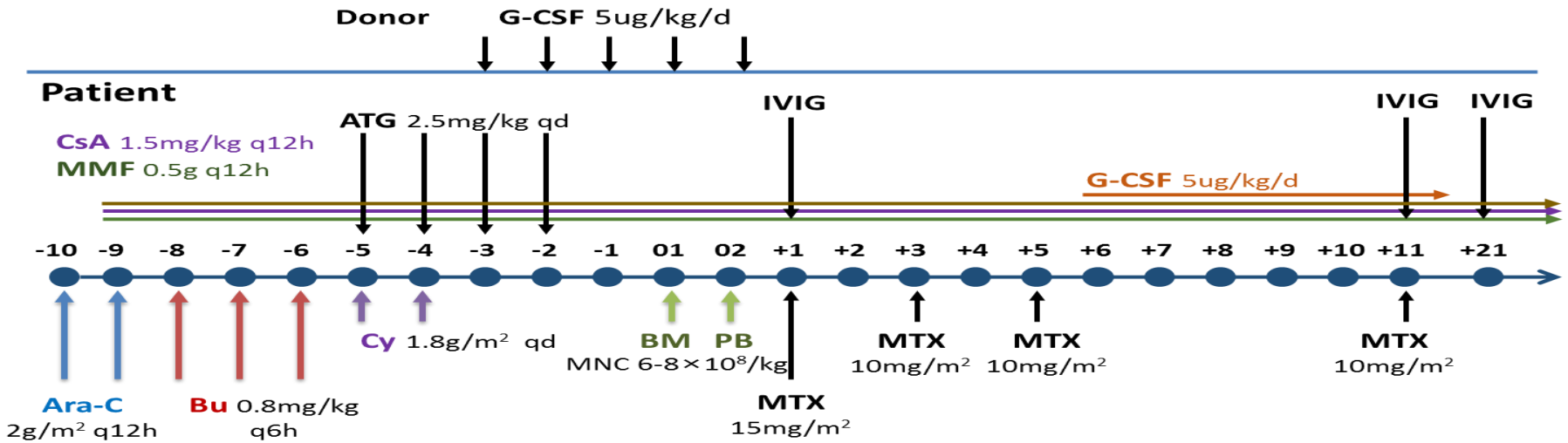
Donor



In vivo T cell regulation (G-CSF)

Patient

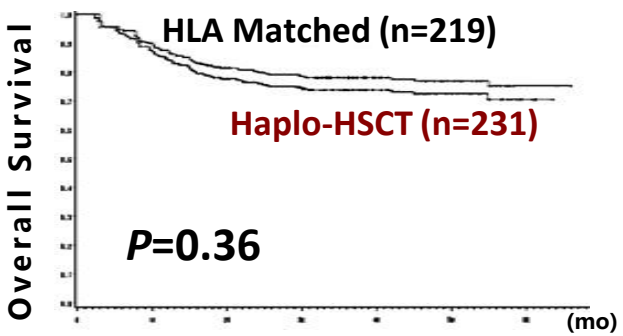
CsA + ATG…



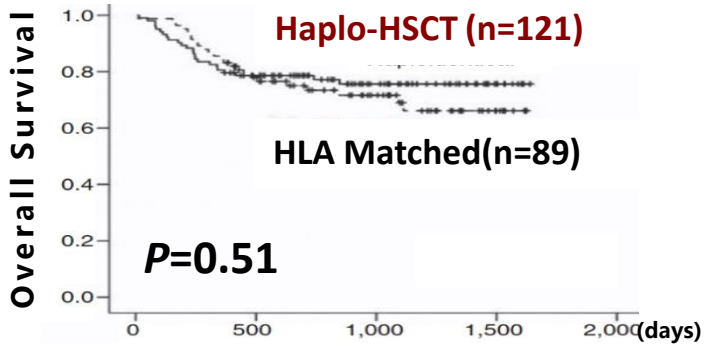
- *Huang XJ, et al. Chin Med J (Engl). 2004*
- *Huang XJ, et al. Bone Marrow Transplant. 2006*

Firstly enabling haplo- comparable to HLA matched HSCT in Malignancy

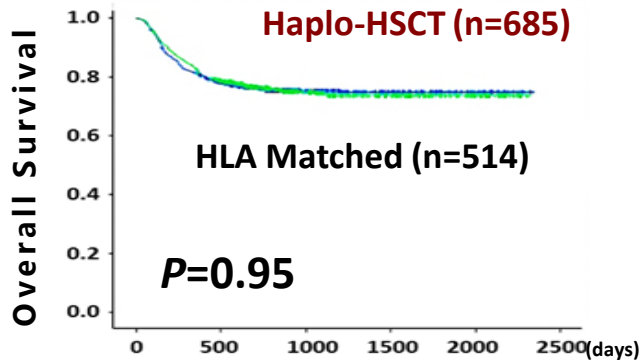
Prospective Multicenter Studies



AML



ALL



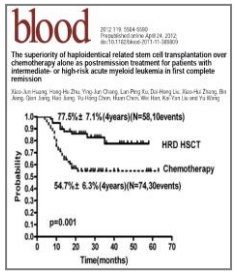
Acute Leukemia

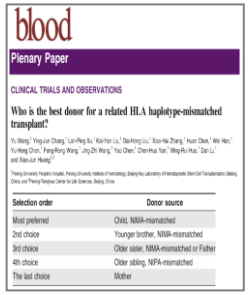
Overturning traditional concept "haplo-SCT is formidable"

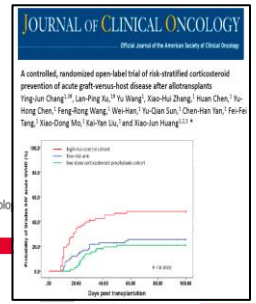
Form basis of new concept "haplo-SCT is feasible"

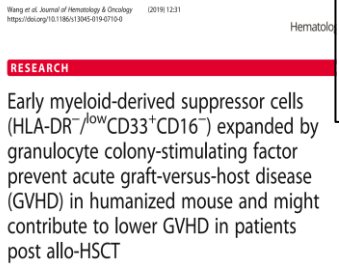
- *Huang XJ. et al. Blood. 2015*
- *Huang XJ. et al. Clin Cancer Res. 2016*
- *Huang XJ. et al. Leukemia. 2018*

Integration of Haplo-HSCT innovations into System Globally Recognized "Beijing Protocol"









Dietger Niederwieser

Jeff Szer

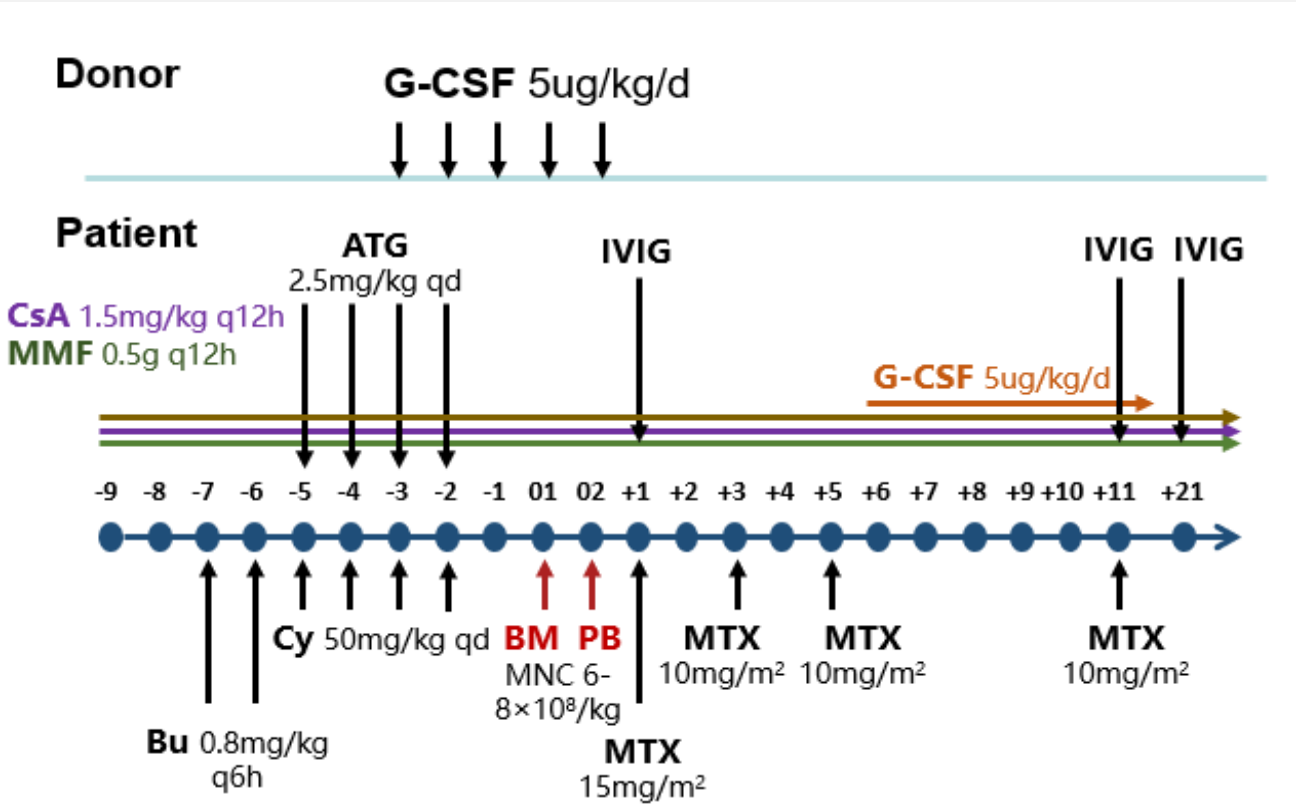
Yoshihisa Kodera

In recent years the Beijing Protocol has been improved in many aspects and developed into an integrated haplo-HSCT system. The indications for haplo-HSCT have been extended from hematological malignancy to include nonmalignant disease such as severe aplastic anemia and

"Beijing Protocol" has developed into an integrated system--
Reliable Treatment for Patients Without HLA-matched Sibling Donor

Apperley J, et al. Biol Blood Marrow Transplant. 2016

G-CSF/ATG based haplo-SCT from leukemia to aplastic anemia



Intensive regimen: Bu + Cy/ATG

Infused graft: G-CSF primed BM + PB

GvHD prophylaxis: CsA, MTX, MMF, ATG

- **N**=19
- **Follow-up:** 746 (90–1970) days
- **Engraftment:**

  WBC: **100%**, 12(10-29) days

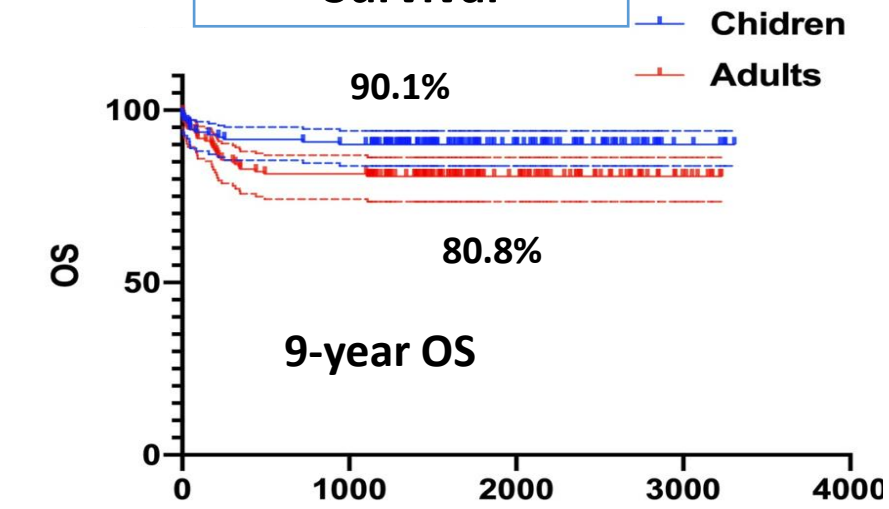
  PLT: 84.2%, 18(8-180) days

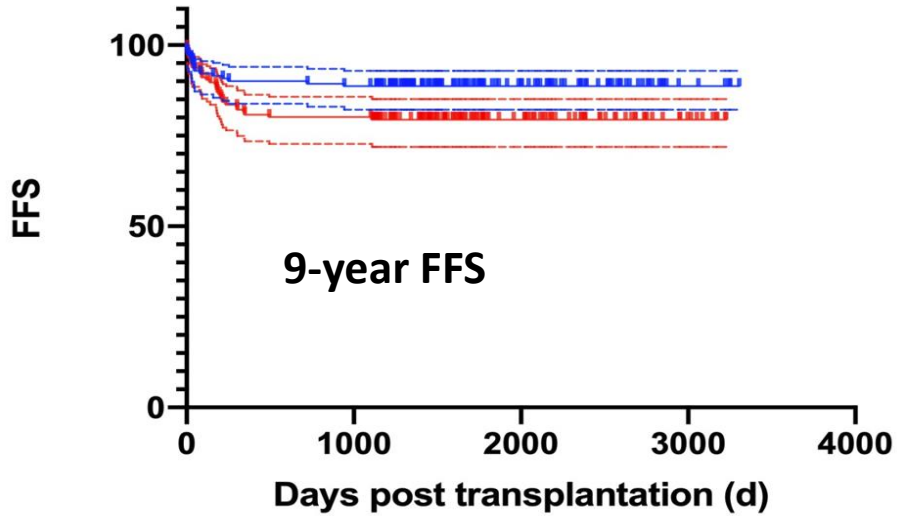
- **III-IV acute GvHD:** 21%

G-CSF/ATG based haplo-SCT extended to SAA: Salvage choice

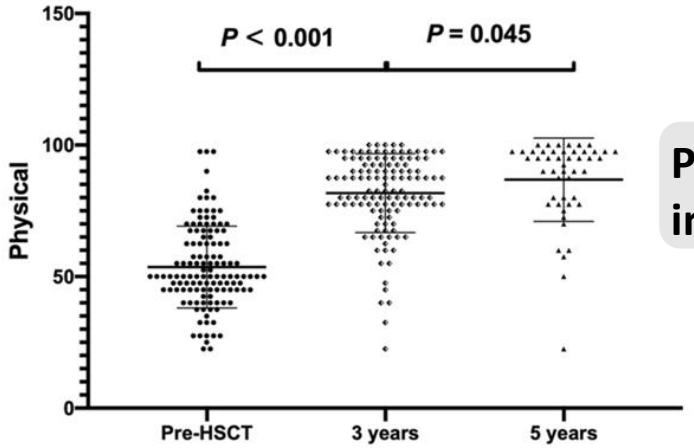
IPIG

Survival

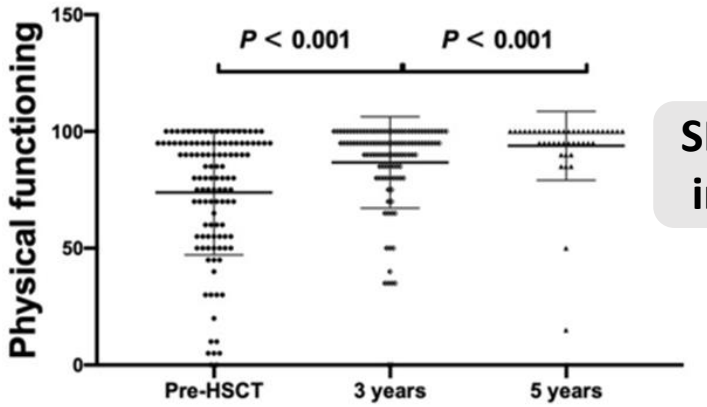




Quality of life



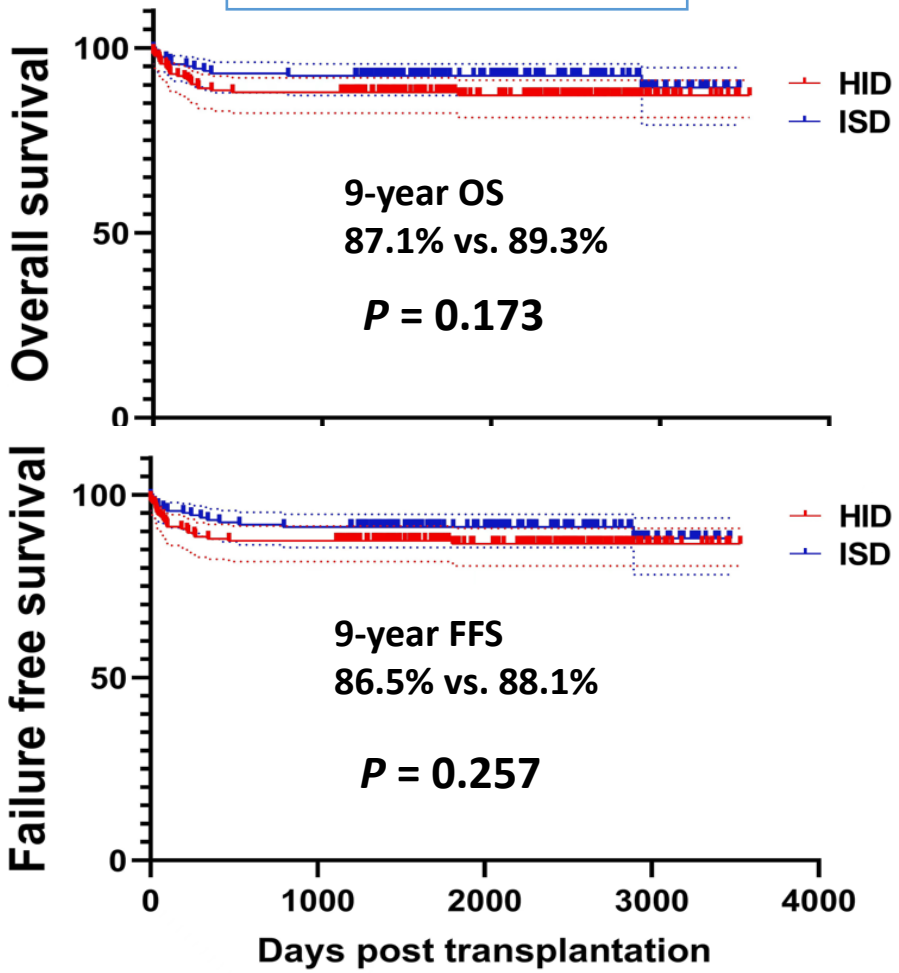
PedsQL 4.0
in children



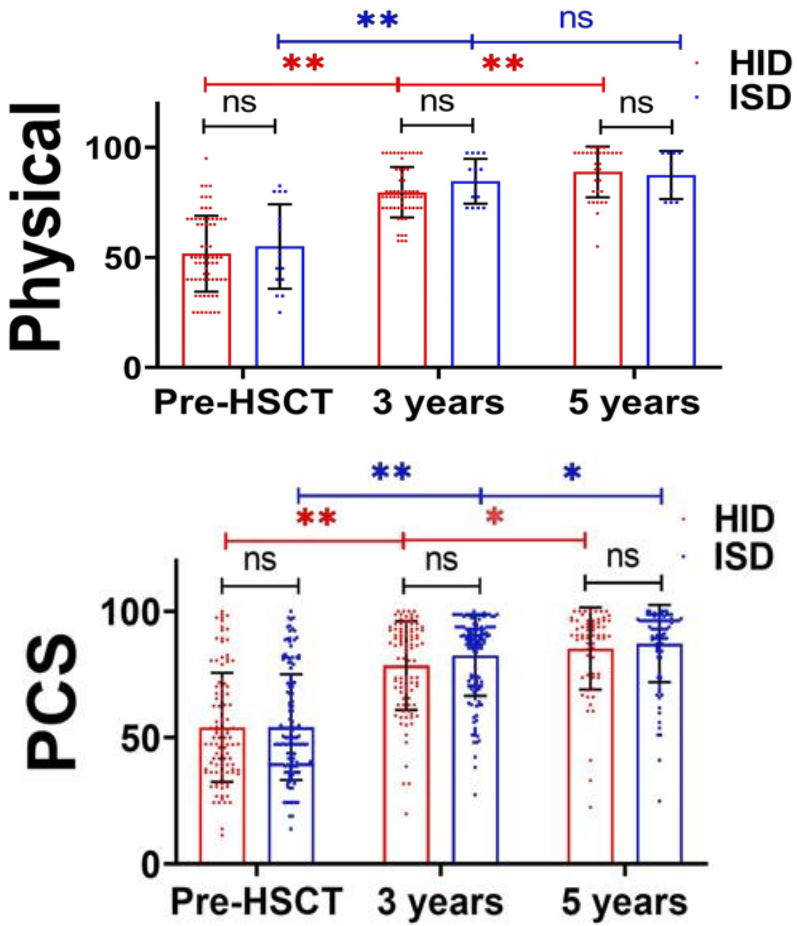
SF-36
in adults

G-CSF/ATG based haplo-SCT extended to SAA: Upfront choice

Survival



Quality of life



PedsQL 4.0
in children

SF-36
in adults

G-CSF/ATG based haplo-HSCT for AA: Expert commentary

Science Bulletin

Prof. Arnon Nagler
Co-Chair of ALWP of the EBMT


Prof. Arnon Nagler

thus no wonder that professor Xiao-Jun Huang and his group pioneered the non T depleted haplo transplants for hematological malignancies in China paving the way for many other transplant centers in the world, establishing the G-CSF primed bone marrow and peripheral blood combined stem cell source be confirmed in additional SAA patient cohorts and in multicenter studies. In conclusion, treatment of severe aplastic anemia including with HSCT has improved significantly over the past 4 decades and the study by Dr. Xu Lang-Ping on behalf of his colleagues from the Peking University People's Hospital and Institute of Hematology, Beijing, China is an important step forward.

The NEW ENGLAND JOURNAL of MEDICINE

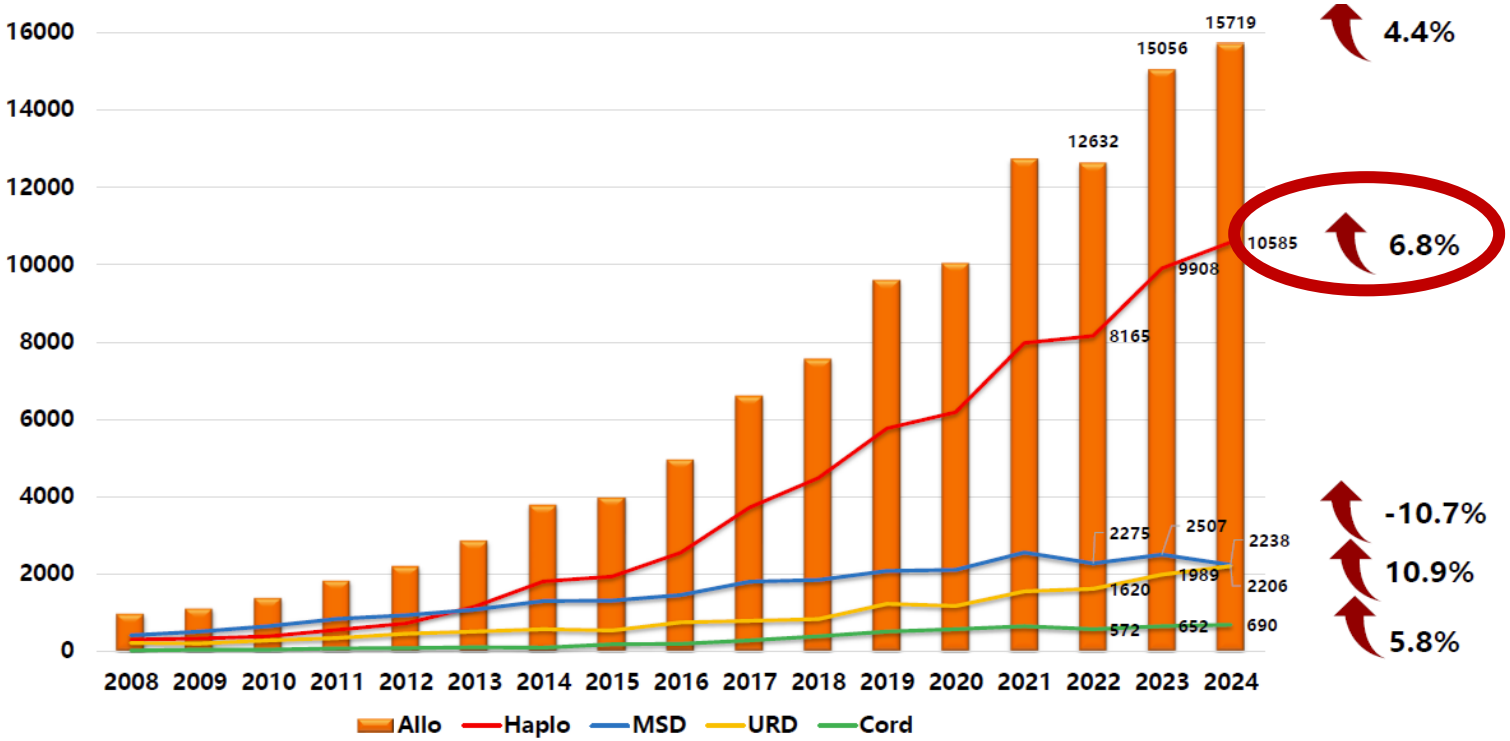
Prof. Neal S. Young
National Institutes Of Health

used to prevent GVHD. The results have been encouraging on the basis of extensive experience in Chinese centers, with much smaller series of transplant recipients in the United States and Europe (Table 3). Haploidentical transplantation has been advocated in China as first-line treatment for children.[92]

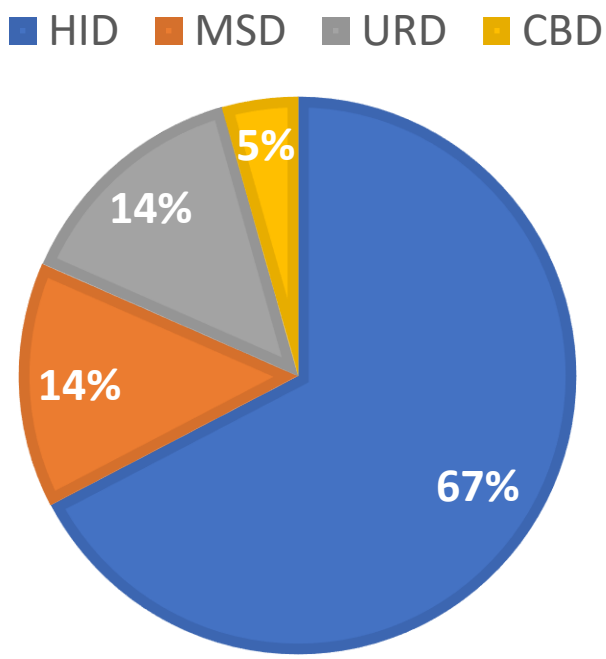
The results have been encouraging on the basis of extensive experience in Chinese centers…

Haplo HSCT has developed rapidly in China

The annul trend of allo-HSCT



Allo-HSCT in 2024



Data from Chinese Blood and Marrow Transplantation Registry Group (CBMTR)

Summary II

- G-CSF/ATG based haploidentical protocol (Beijing Protocol) has led to inspiring survival in leukemia and aplastic anemia.
- Could haplo-SCT extend to Paroxysmal Nocturnal Hemoglobinuria?

Content

1 The evolution of HSCT in Paroxysmal Nocturnal Hemoglobinuria

2 The development of G-CSF/ATG based haploidentical protocol

3 **Haploidentical HSCT for PNH**

The G-CSF/ATG based haplo-HSCT in PNH: initial experience

Case	Engraftment (days) ANC >0.5 × 10^9/L	Engraftment (days) PLT >20 × 10^9/L	Full-donor chimerism (days)	GVHD Acute	GVHD Chronic	Follow-up (months)/ Outcome
1	15	33	34	Grade I	Limited	21/Alive
2	11	13	28	Absent	Absent	19/Alive
3	12	20	30	Grade I	Limited	14/Alive
4	13	28	36	Absent	Limited	15/Alive
5	12	18	32	Absent	Limited	29/Alive
6	First transplant: graft failure		–	–	–	6/Dead (infection)
	14	23	42	Grade II	Absent	
7	12	18	32	Grade III	Limited	15/Alive
8	12	15	40	Absent	Absent	17/Alive
9	12	14	34	Grade II	Extensive	20/Alive
10	11	13	34	Grade II	Absent	17/Alive

Haplo-HSCT:

9/10 alive and transfusion-independent

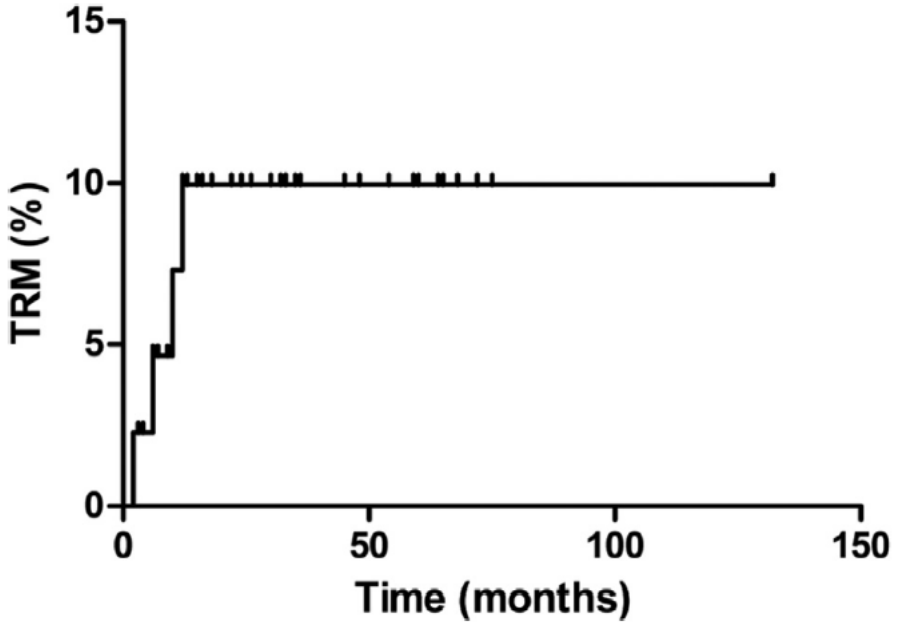
4 II/III aGVHD

5 limited cGVHD, 1 ex cGVHD

The G-CSF/ATG based haplo-HSCT in PNH: single center experience

Conditioning regimen of classic PNH, n (%)	
Fludarabine + Cy + ATG	8 (53.33)
Bu + Cy + ATG	7 (46.67)
Conditioning regimen of PNH-AA syndrome, n (%)	
Fludarabine + Cy + ATG	7 (24.14)
Bu + Cy + ATG	22 (75.86)
Donor type, n (%)	
HLA-identical sibling	15 (34.09)
HLA-MUDs	4 (9.09)
HLA-haplo-donors	25 (56.82)
GVHD prophylaxis, n (%)	
CsA (HLA-identical sibling)	15 (34.09)
CsA + MMF + MTX	
HLA-MUDs	4 (9.09)
HLA-haplo-donors	25 (56.82)

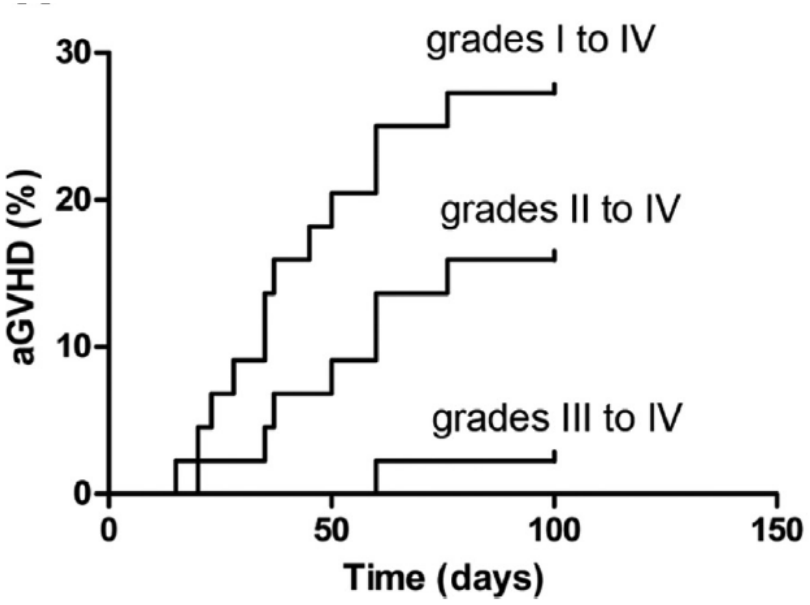
44 PNH cases from one center
The 1-year transplant-related mortality was 9.95%



The causes of TRM included GVHD in 1 case, TMA in 1 case, and infection in 2 cases

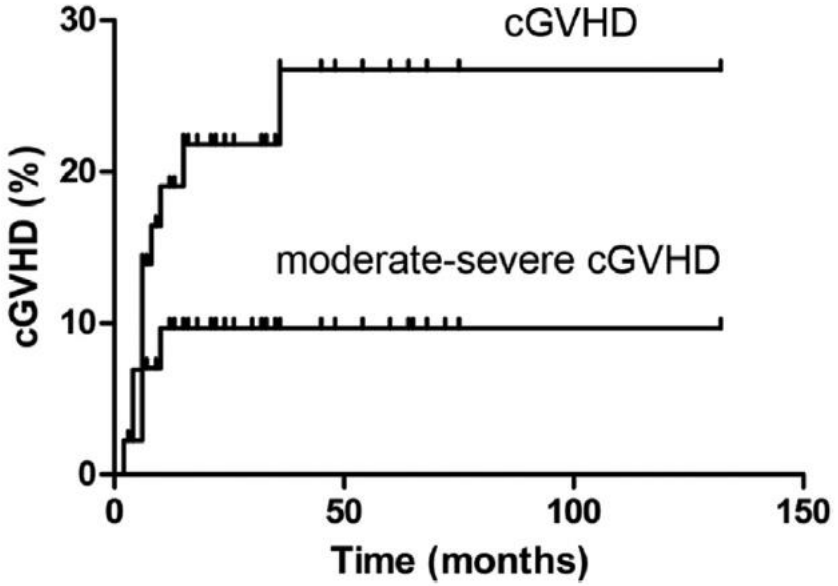
The G-CSF/ATG based haplo-HSCT in PNH: single center experience

aGVHD



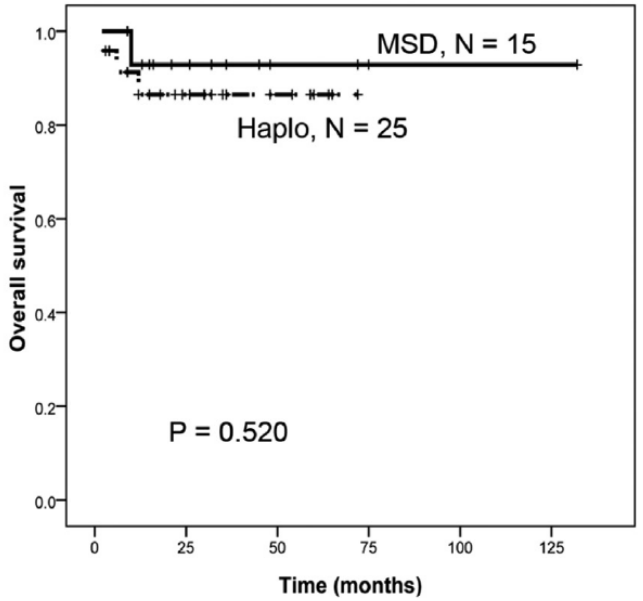
Grades I to IV: 27.27%
Grades II to IV: 15.91%
Grades III to IV: 2.27%

cGVHD



cGVHD: 26.73%
Moderate to severe cGVHD: 9.70%

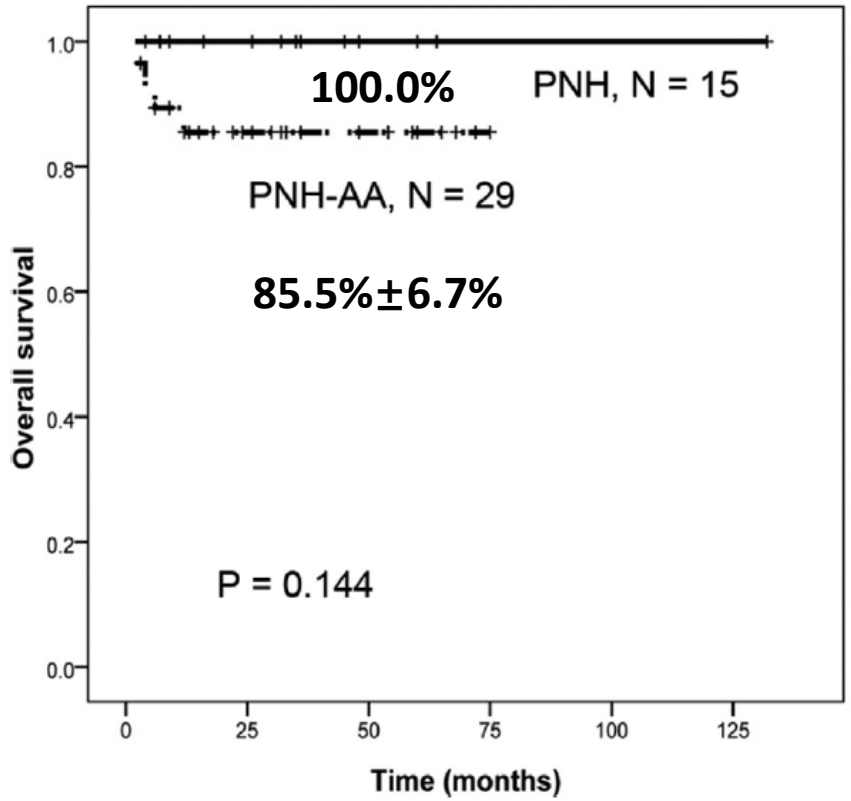
OS



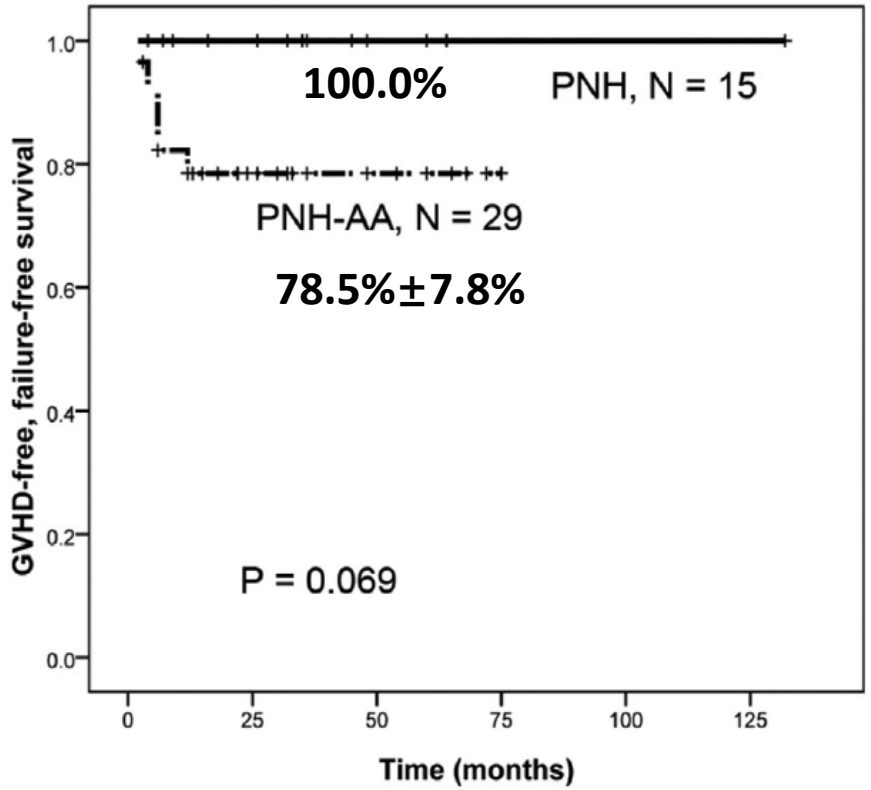
HID: 86.5%±7.3%
MSD: 93.3%±6.4%

The G-CSF/ATG based haplo-HSCT in PNH: single center experience

OS



GFFS



PNH: classic PNH

PNH-AA: clinical PNH (PNH clone > 5%) with aplastic anemia (AA)

The comparison of haplo-HSCT and MSD in PNH: multicenter study

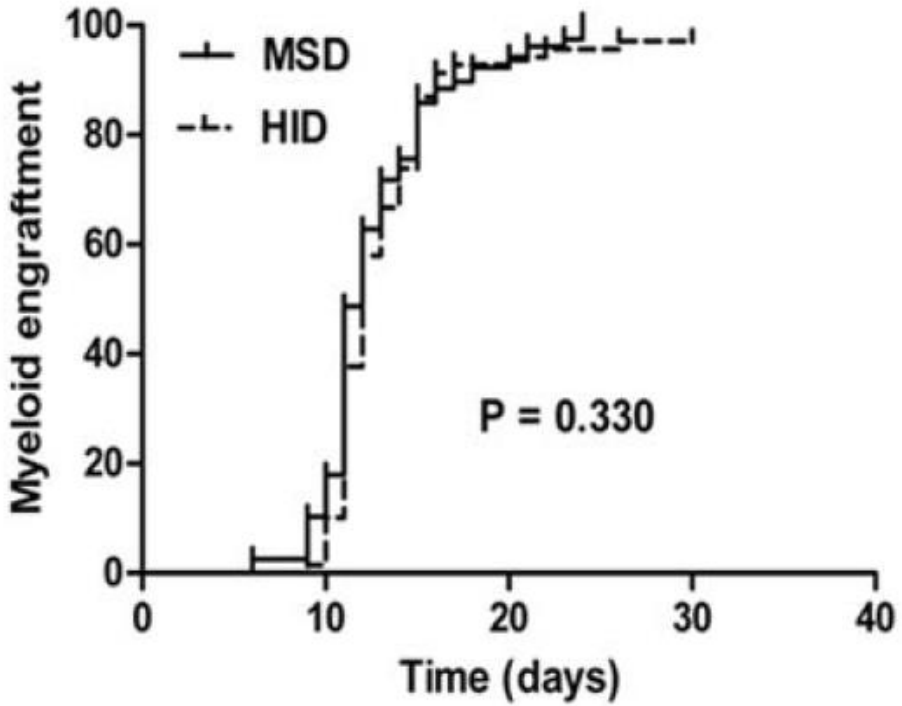
Multicenter study in China

- 151 patients from 10 centers
- HSCT from year of 2002 to 2021
- HID: n=73
- MSD: n=78
- **All haplo- applied G-CSF/ATG based protocol**

Variable	HID ($n = 73$)	MSD ($n = 78$)	P
Clinical characteristics			
Median age, years (range)	23 (6–54)	30 (14–50)	0.100
≤ 20 years, no. (%)	20 (27.40)	11 (14.10)	0.039
21–39 years, no. (%)	34 (46.58)	46 (58.97)	0.127
≥ 40 years, no. (%)	19 (26.03)	21 (26.92)	0.901
Gender (male/female)	42/31	52/26	0.247
Classification of PNH at transplantation, no. (%)			
Classical PNH	13 (17.81)	27 (34.62)	0.019
PNH in the setting of another BM disorder			
PNH-AA syndrome	59 (80.82)	48 (61.54)	0.009
PNH-MDS	0 (0.00)	3 (3.85)	0.267
PNH-AML	1 (1.37)	0 (0.00)	0.483

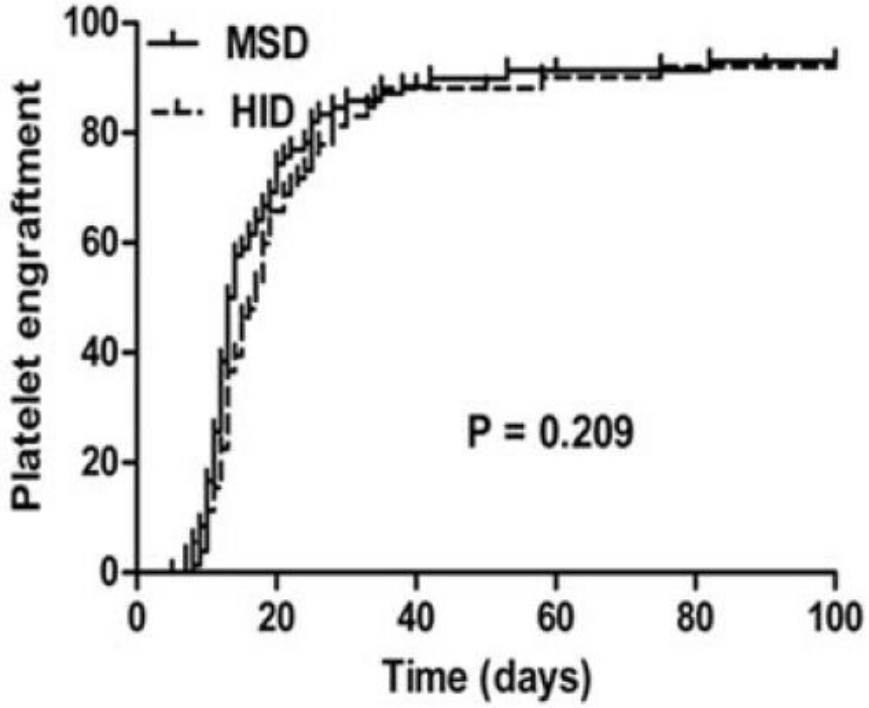
Similar incidence of engraftment between haplo-HSCT and MSD in PNH

Myeloid engraftment



HID: 97.10% ± 2.02%
MSD: 100.00 %

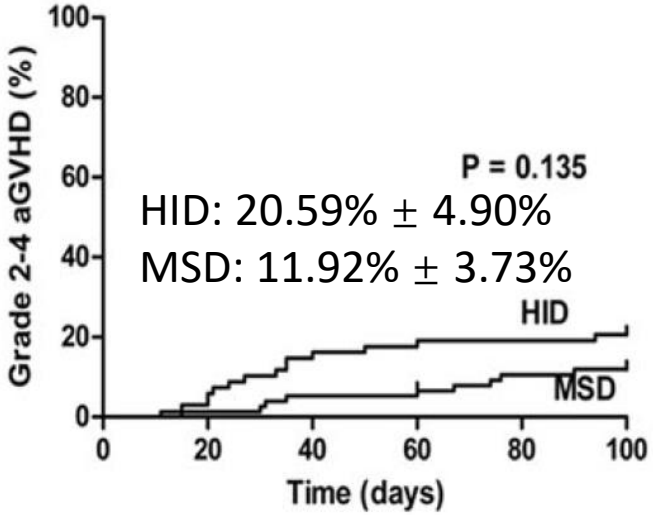
Platelet engraftment



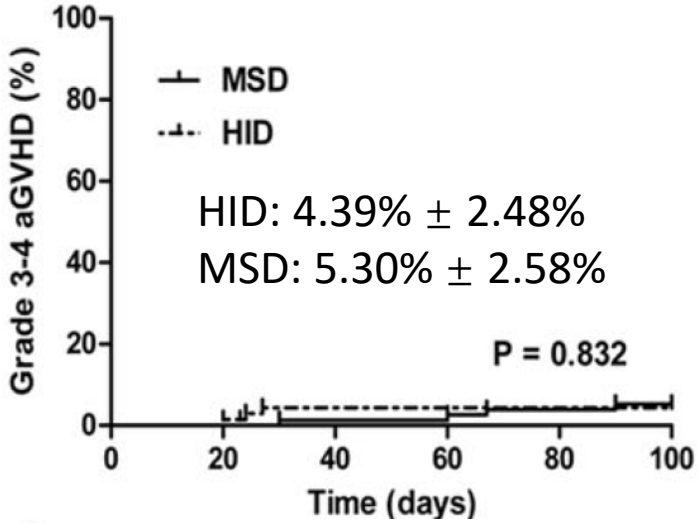
HID: 92.07% ± 3.56%
MSD: 97.69% ± 2.14%

Similar incidence of GVHD between haplo-HSCT and MSD in PNH

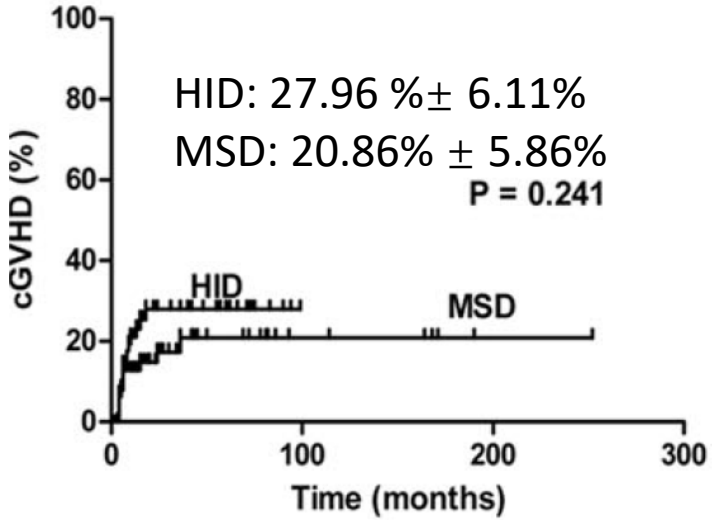
2-4 aGVHD



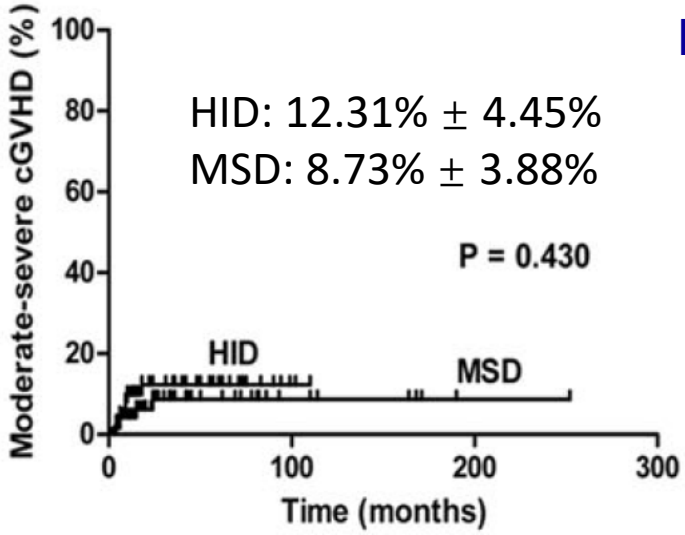
3-4 aGVHD



cGVHD

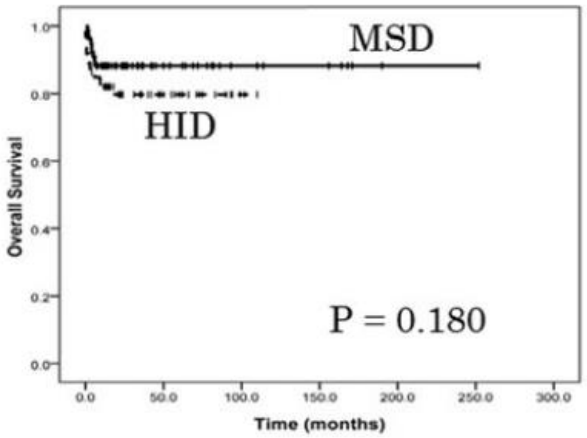


Moderate-severe cGVHD



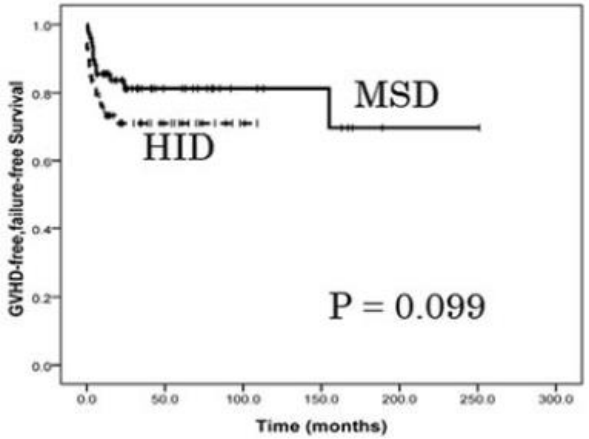
Similar Survival rates between haplo-HSCT and MSD in PNH

OS in whole cohort



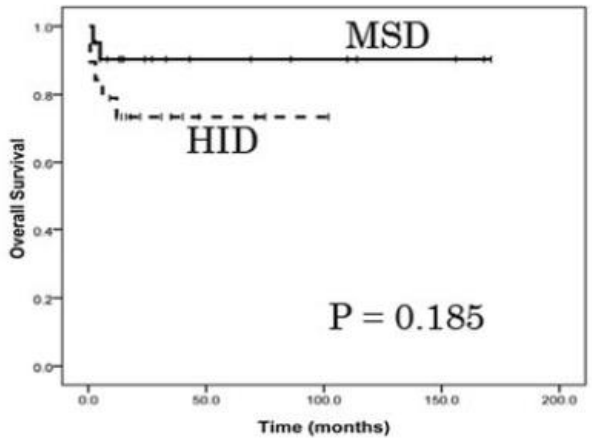
HID: 79.7% ± 4.9%
MSD: 88.2% ± 3.7%

GFFS in whole cohort



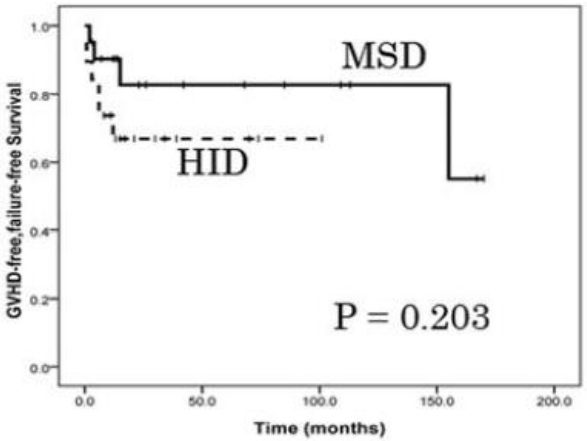
HID: 71.0% ± 5.6%
MSD: 81.2% ± 4.9%

OS in patients ≥40 years



HID: 73.3% ± 10.2%
MSD: 90.2% ± 6.6%

GFFS in patients ≥40 years



HID: 67.0% ± 11.2%
MSD: 82.7% ± 9.4%

The indication of HSCT treating PNH in China

Guidelines for the diagnosis and management of PNH (2024)

Chinese Society of Hematology

- **Failure of complement inhibitor therapy**
- **Severe classic PNH in which complement inhibitors are not accessible**
- **PNH with severe/refractory bone marrow failure**
- **PNH evolving into MDS or acute myeloid leukemia**

*Unlike the Chinese guidelines, other current international guidelines recommend that transplant candidates should have an HLA-matched sibling donor.

The indication of HSCT treating PNH in China

The consensus from The Chinese Society of Hematology

Zhang *et al. J Hematol Oncol* (2021) 14:145
https://doi.org/10.1186/s13045-021-01159-2

Journal of Hematology & Oncology

REVIEW Open Access

The consensus from The Chinese Society of Hematology on indications, conditioning regimens and donor selection for allogeneic hematopoietic stem cell transplantation: 2021 update

- **Patients with SAA/PNH who fail to respond to one course of IST**
- **PNH patients who develop clonal evolution, resulting in MDS/AML**

PTCy based Haplo-HSCT in PNH with limited cases

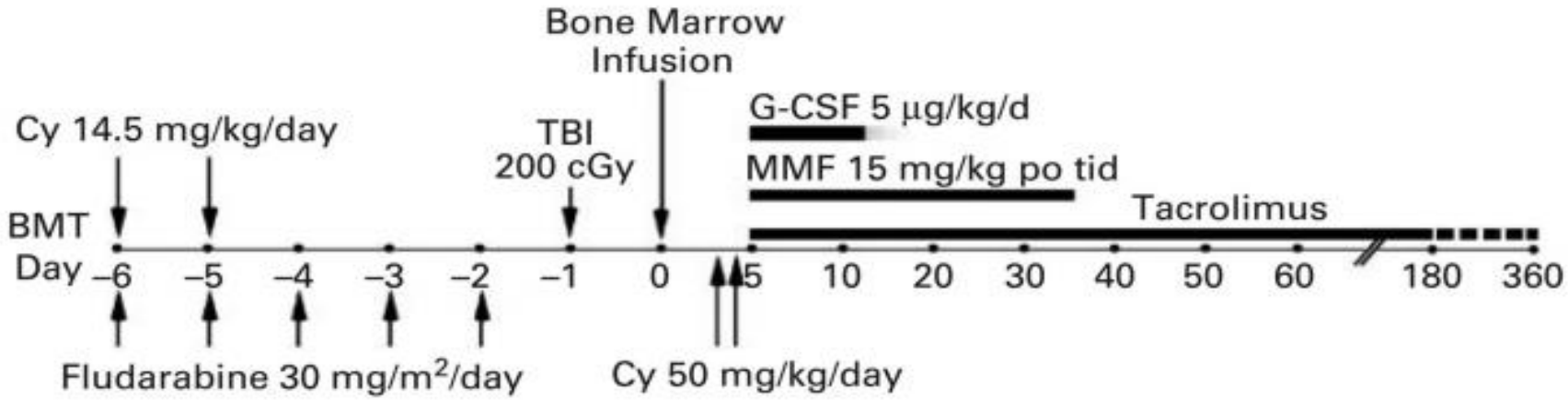


Figure 1.
Treatment schema. CY = cyclophosphamide; MMF = mycofenolate mofitil; TBI = total body irradiation.

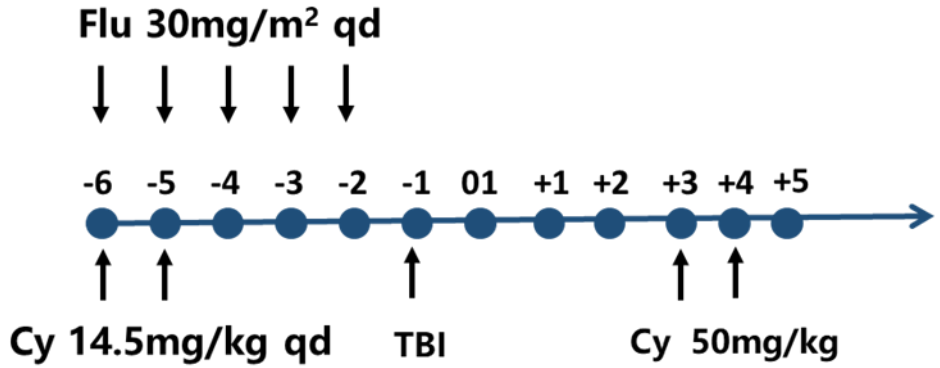
3 patients with thrombotic PNH

1 patient died of infection on +8d

2 patients achieved sustained engraftment and DFS

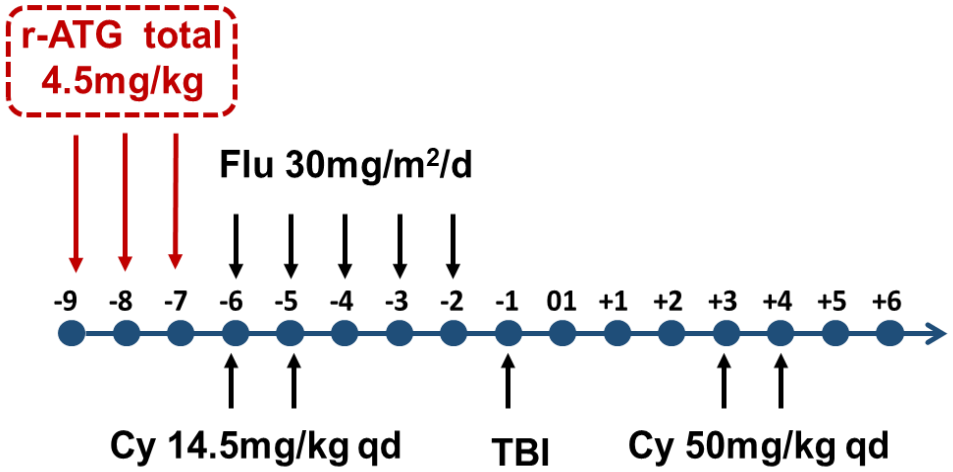
Modified PTCy by adding low dose ATG based haplo-SCT in SAA

Traditional



- 2011---2017, N=33
- Engraftment: 67%
- 2-year OS: 78%

Modified



- 2017---2020, N=32
- Engraftment: 94%
- 1-year OS: 81%

Summary III

- Haplo-HSCT with PTCy based protocol has limited cases in non-malignancy
- Haplo-HSCT has curative role in management of PNH with an acceptable survival rate, data mainly from G-CSF/ATG based protocol
- Haplo-HSCT may be a viable option for patients with PNH who lack HLA-matched donors

IPIG
International PNH Interest Group

THANK YOU!