Wisdom of the Land

HSCT in childhood leukemia

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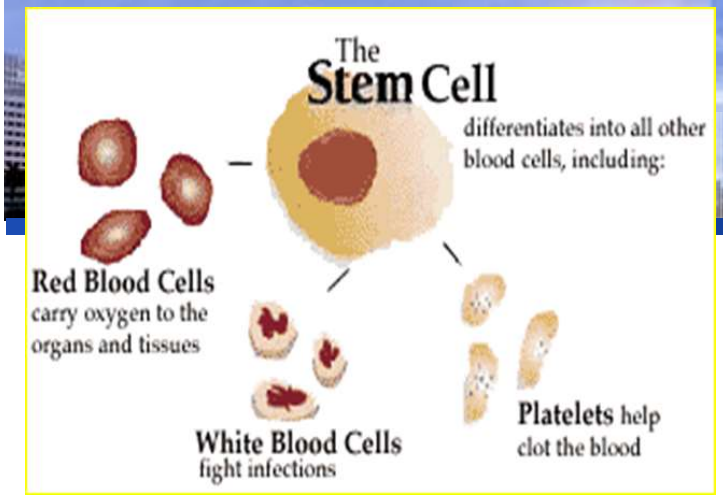
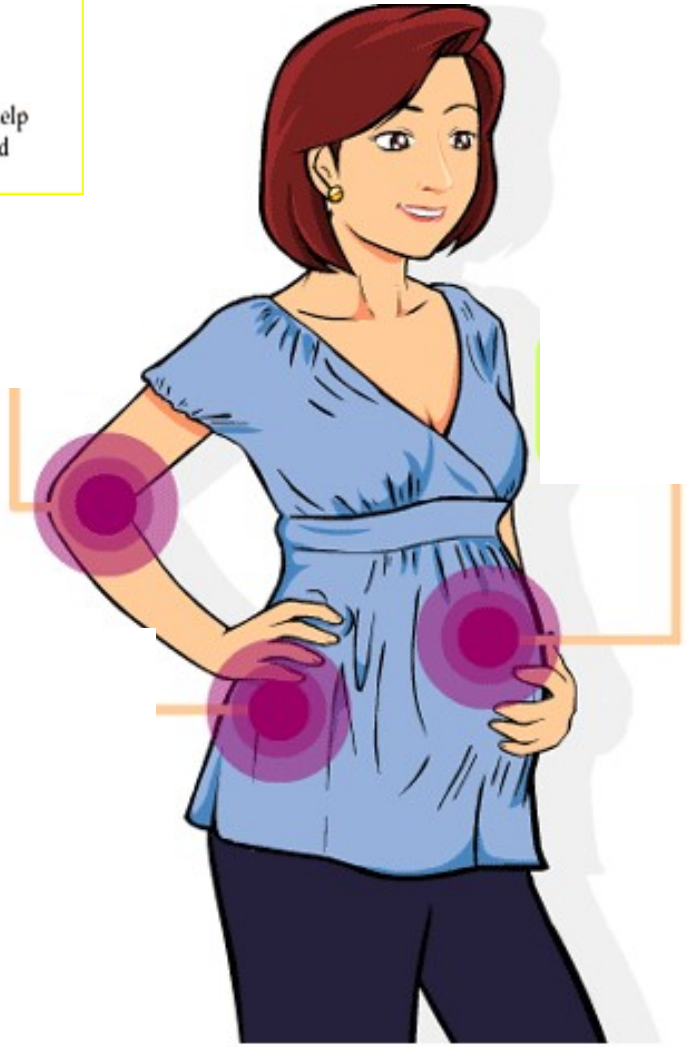
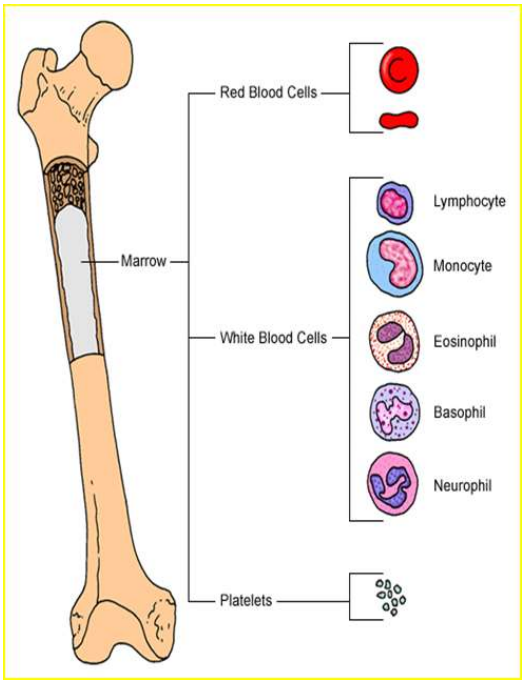
Topics outline

- Overview principles of HSCT
- Indications of HSCT in childhood leukemia
- Complications post-HSCT
- Outcome of HSCT in leukemia
- Targeted therapy and HSCT
- Conclusion

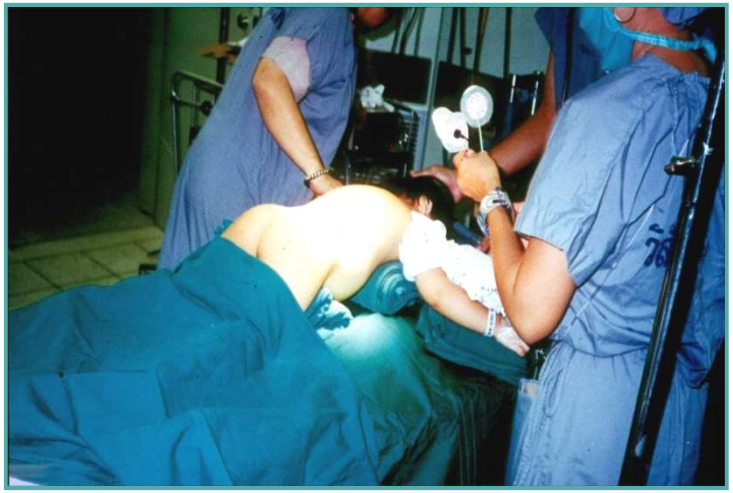
Sources of HSC

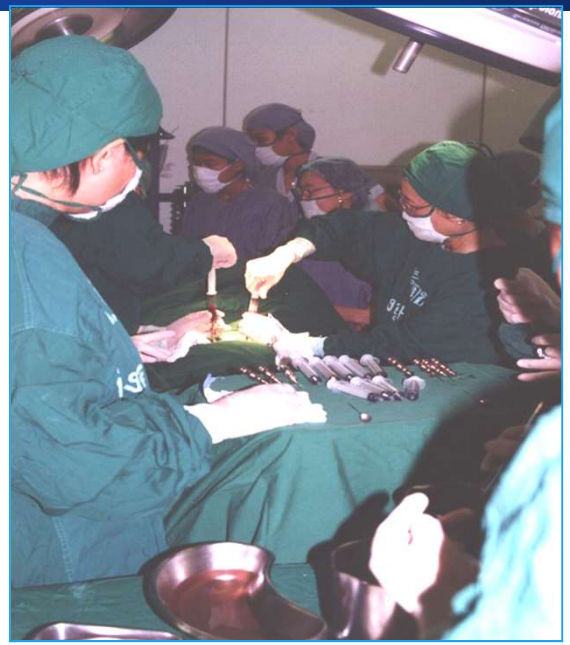


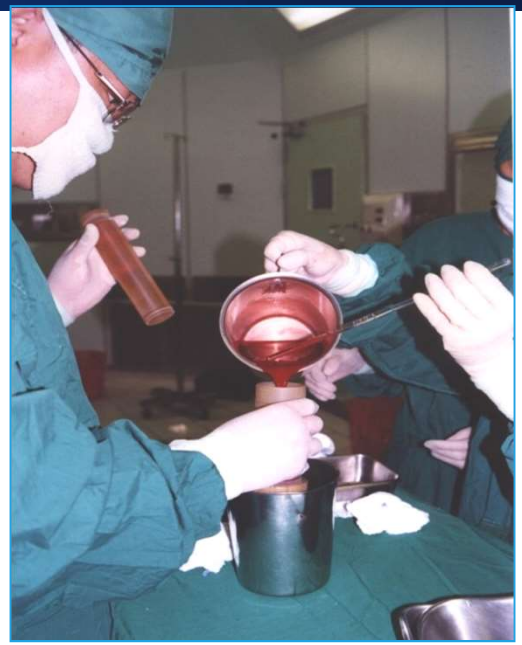


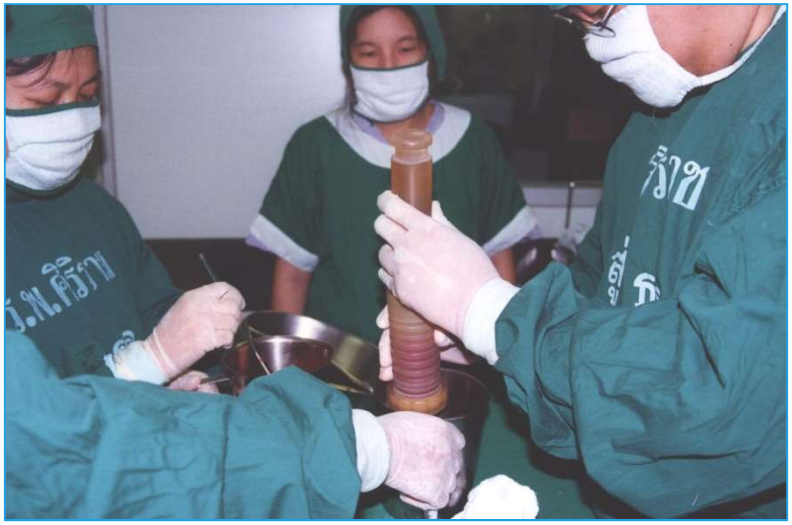


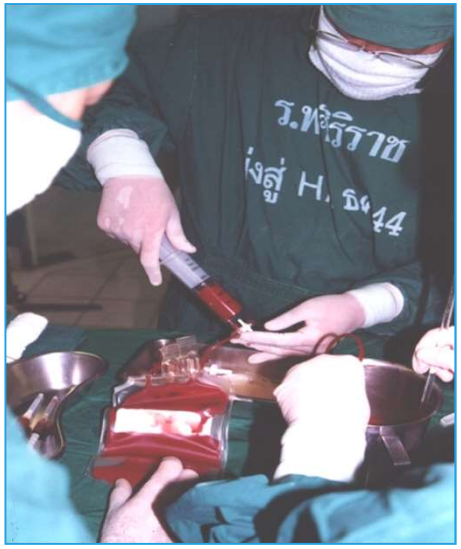
BMSC collection



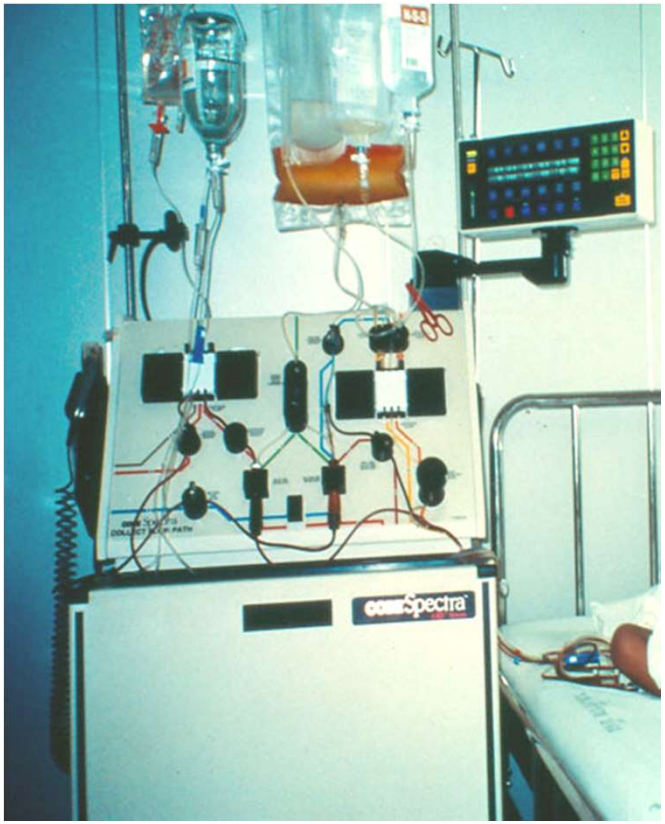


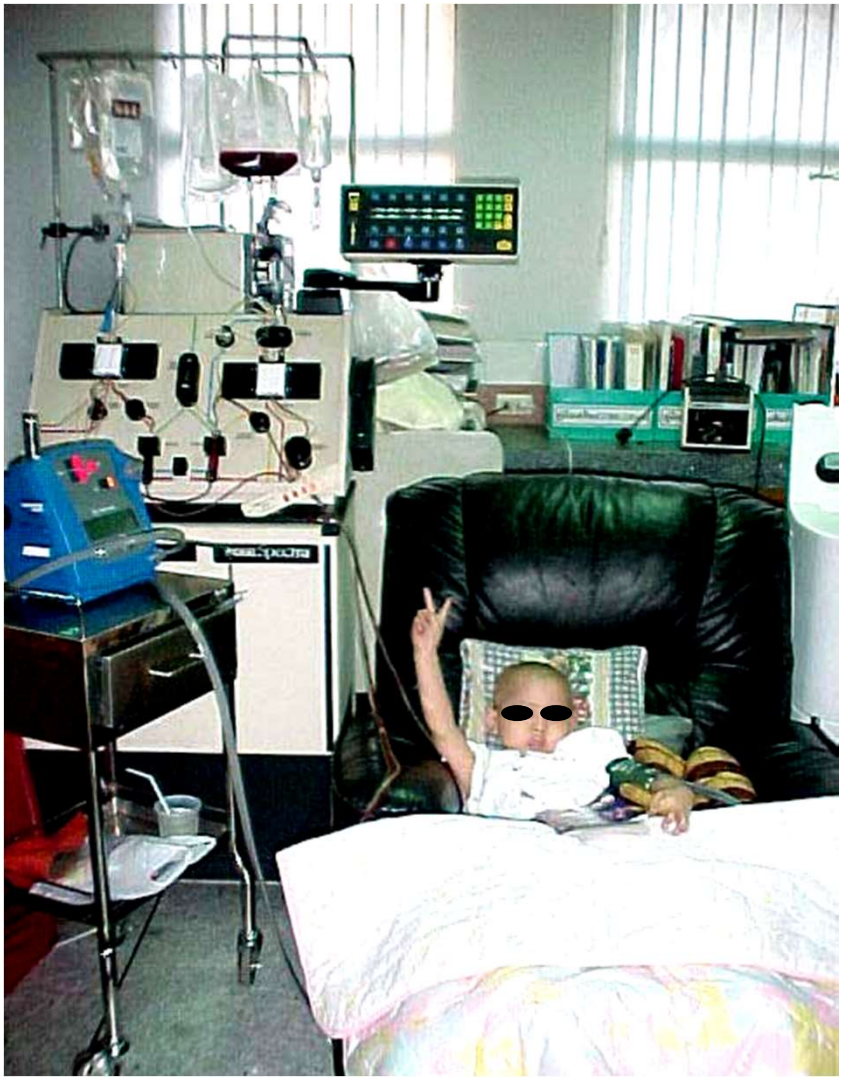




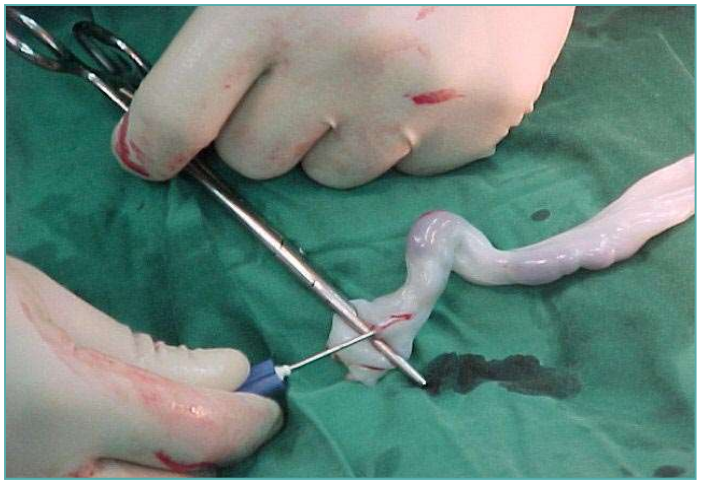


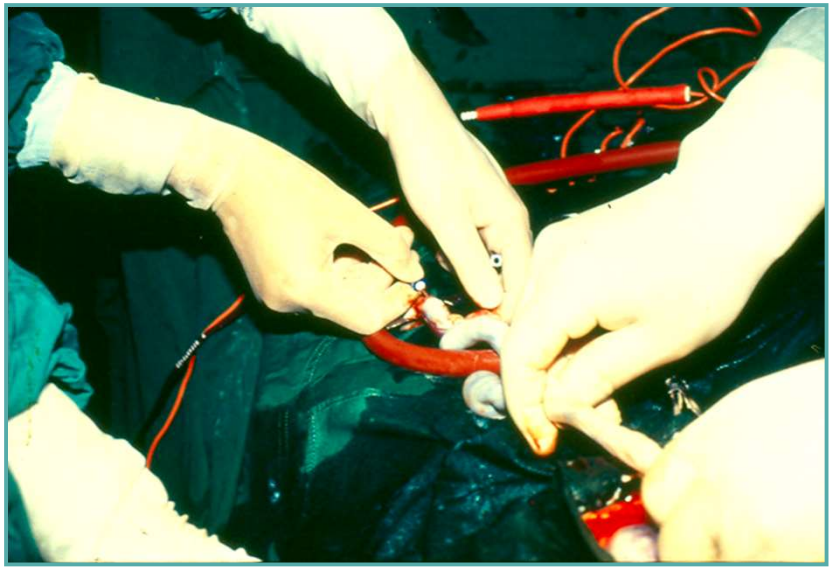
PBSC collection





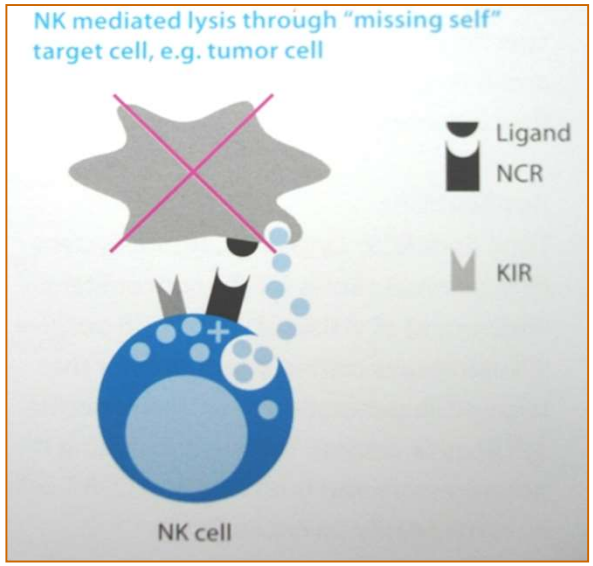
CBSC collection





Advantages of HSCT in leukemia

- Allow higher and more effective doses of chemoRx to eradicate the malignant cells before rescue the BM function with normal HSC
- Offer immunotherapy (Graft versus leukemia effect) that can eradicate chemoresistant leukemic cells: CML > AML > ALL



Types of HSCT

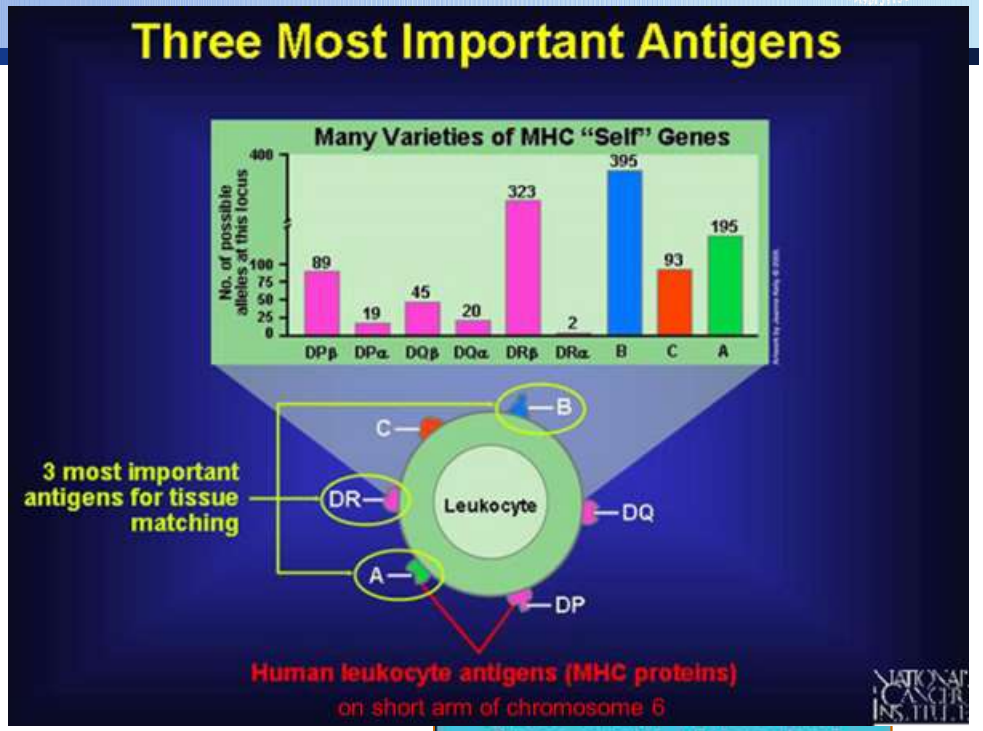
Allogenic HSCT

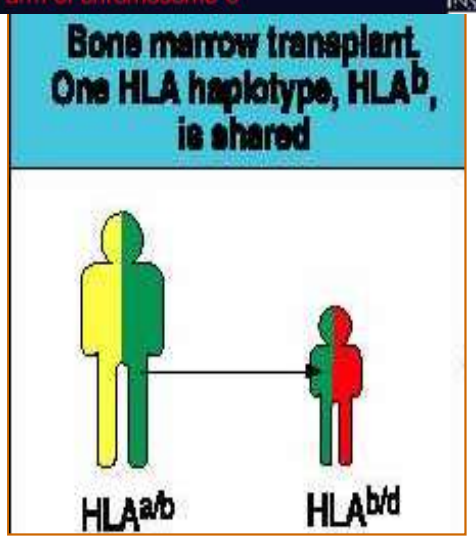
2.1 Related allogenic SCT

2.2 Syngenic SCT

2.3 Unrelated allogenic SCT

2.4 Haploidentical SCT





Unrelated HSCT

- Aim : expand donor pools → increased possibility to find matched unrelated donor

  (1 : 25,000 – 50,000)

- Important points : improve HLA matching system

  expand donor pools

  financial support 2,121,000 baht

ประกาศศูนย์บริการโลหิตแห่งชาติ สภากาชาดไทย

ที่ 4 /2561

เรื่อง หลักเกณฑ์ อัตรา และเงื่อนไข การเบิกค่าใช้จ่ายจากเงินงบประมาณ

โครงการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดโลหิตจากผู้บริจาคที่ไม่ใช่ญาติ

ปีงบประมาณ 2562

วันที่ 1 พฤศจิกายน 2561

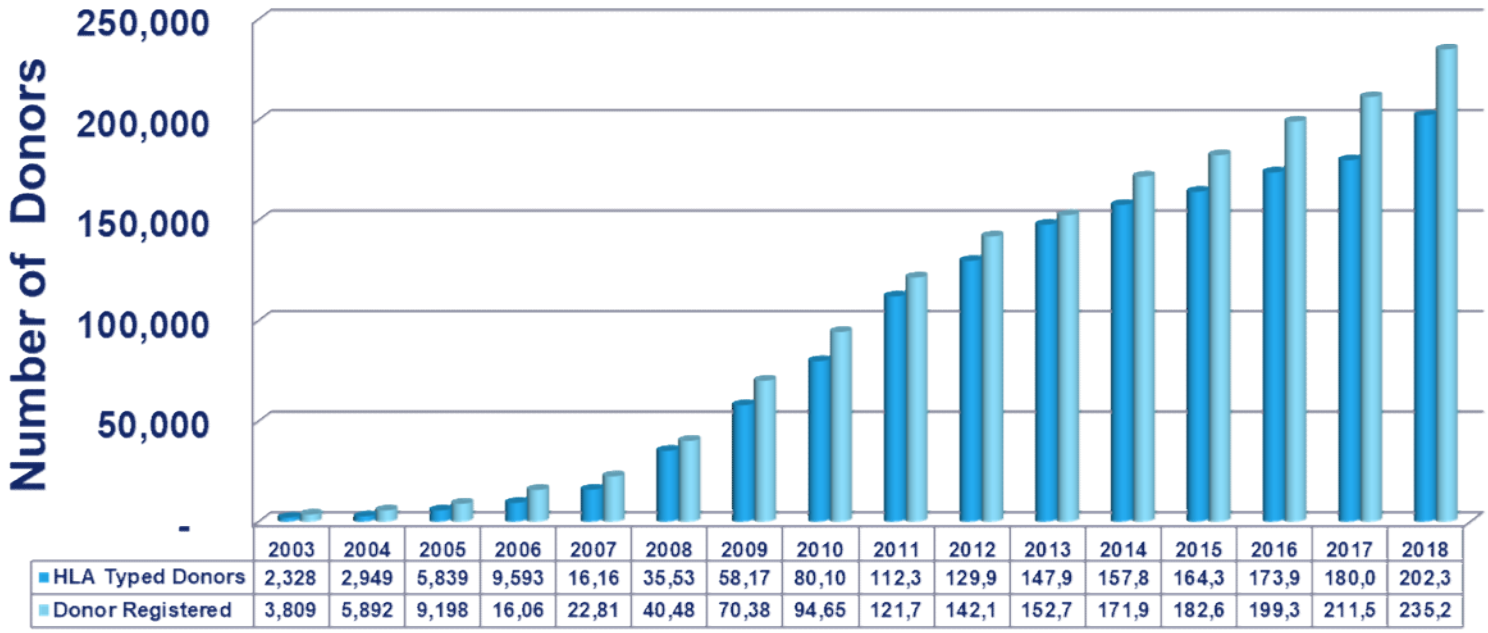
Coverage of HSCT

- สปสช. เริ่มโครงการดูแลค่าใช้จ่าย HSCT ปี 2551 : คณะกรรมการหลักประกันสุขภาพแห่งชาติ เมื่อวันที่ 7 มกราคม 2562 มีมติให้ coverage สำหรับ Allogenic HSCT 1,300,000 บาท/ราย
- สำหรับ Unrelated HSCT ศูนย์บริการโลหิตแห่งชาติฯ สนับสนุนงบประมาณให้ผู้ป่วยกรณีมีค่าใช้จ่ายส่วนต่างที่ยังไม่คลอบคลุมโดยสิทธิหลักประกันสุขภาพแห่งชาติ โดยประมาณ 800,000 บาท/ราย และสิทธิข้าราชการสนับสนุนงบประมาณกรณี donor 300,000 บาท/ราย

Stem Cell Donor in Registry (December 2018)

Started in May, 2002 at National blood center, Thai Red Cross Society

	December 2018
HLA typed donors	202,393
Registered donors	235,241



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
HLA Typed Donors	2,328	2,949	5,839	9,593	16,16	35,53	58,17	80,10	112,3	129,9	147,9	157,8	164,3	173,9	180,0	202,3
Donor Registered	3,809	5,892	9,198	16,06	22,81	40,48	70,38	94,65	121,7	142,1	152,7	171,9	182,6	199,3	211,5	235,2

Courtesy of Ms.Pavinee et al; National blood center, Thai Red Cross Society

Transplant Patients Diagnosis (December 2018)

Leukemia	150
Thalassemia	75
Myelodysplastic Syndrome (MDS)	22
Lymphoma	15
Aplastic Anemia	15
Chronic Myelomonocytic Leukemia (CMML)	3
Juvenile Myelomonocytic Leukemia (JMML)	3
Acute Promyelocytic Leukemia (APL)	2
Chronic Granulomatous Disease (CGD)	2
Diamond-Blackfan Anemia	2
Hemophagocytic Lymphohistiocytosis (HLH)	3
Primary Myelofibrosis (PMF)	2
Adrenoleukodystrophy Disease (ALD)	2

Autoimmune Colitis	1
Autoimmune Lymphoproliferative Disorder	1
Congenital Pure Red Cell Aplasia	1
Gaucher Disease	1
Griscrlli Syndrome	1
Hemoglobin Tak Disease	1
Hyper IgM Syndrome	1
Juvenile Myelomonocytic Leukemia (JCML)	1
Multiple Myeloma (MM)	1
Myelofibro Myeloid Metaplasia (MFMM)	1
Refractory anemia with excess of blasts	1
SCID	1
Wiskott-Aldrich syndrome (WAS)	1

Haploidentical HSCT

Table 1: Outcome of T cell depleted haploidentical transplantation for children with acute leukemia.

Ref.	Patients with AL (total)	Age range (years)	Disease status	Conditioning	Graft manipulation	Graft composition CD34 ($\times 10^6$)	Graft composition CD3 ($\times 10^7$)	Engraftment (%)	Acute GVHD (%)	Chronic GVHD (%)	NRM (%)	Relapse (%)	Overall survival (%)
Aversa et al. (1998) [17]	43	4–53	Advanced	FLU/TT/ATG/TBI	CD34 selection	14	2.7	95.3%	None	None	40%	AML: 13% ALL: 63%	AML: 36% ALL: 17%
Handgretinger et al. (2001) [18]	21 (39)	(0.5–18)	NR = 9 CR = 12	MA	CD34 selection	20.7	1.5	92.3%	5%	None	28%	33%	NR: 14% CR: 39%
Goldman et al. (2000) [39]	52	1–19	AML Rel./Ref.	TBI: 40 Non-TBI: 12	Bone marrow CD2 depletion	MNC$\times 10^8$	3.04	71%	44%	None	71%	26%	2%
Ortin et al. (2002) [23]	16 (21)	2–16	CR	CY/TBI	CD34 selection	8.5	5.6	100%	43%	25%	4.8%	18.7%	81.3%
Marks et al. (2006) [22]	34	1–16	CR 18 NR 16	CY/TBI/Campath/ATG	CD34 selection	13.8	0.3–5.2	91.7%	29%	12%	29.4%	CR: 13% NR: 100%	26% AML CR: 28% ALL CR: 38%
Klingebiel et al. (2010) [24]	127	0.6–16	ALL NR 25 CR 102	MA	CD34 selection	12.3	5.0	91%	37%	16.7%	37%	36%	CR: 22–39% NR: 0%
Leung et al. (2011) [38]	38	<16	NR 5 CR 30	TBI: 20Non-TBI: 15	CD34 selection: 13 CD3 depletion: 17 Others: 5	NA	9–44	NA	25.7%	NA	23.9%	14.7%	<2002: 19% >2002: 88%
Lang et al. (2014) [36]	46	1.1–23.7	NR 20 CR 26	FLU/TT/MEL +ATG/OKT3	CD3/19 depletion	14.5	0.59	81.6%	26%	21%	10.8%	38%	CR: 31% NR: 20%
Lang et al. (2015) [43]	29 (41)	<16	NR 9 CR 20	NA	TCRα/β and CD3 depletion	14.9	1.69	88%	24%	18%	NA%	47.2%	CR1–CR3: 100% NR: 0%

AL: acute leukemia; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; ATG: antithymocyte globulin; CR: complete remission; CY: cyclophosphamide; GVHD: graft-versus-host disease; FLU: Fludarabine; MA: myeloablative conditioning; Mel.: Melphalan; NR: not in remission; NRM: nonrelapse mortality; Ref.: refractory; Rel.: relapsed; TBI: total body irradiation; TT: thiotepa.

Jaiswal SR, Chakrabarti S. Advances in Hematology 2016

Table 2: Outcome of haploidentical transplantation for children with acute leukemia without T cell depletion.

Ref.	Number of patients with AL (total)	Age range (years)	Disease status	Conditioning	Graft composition CD34 ($\times 10^6$)	Graft composition CD3 ($\times 10^7$)	GVHD prophylaxis	Engraftment (%)	Acute GVHD (%)	Chronic GVHD (%)	NRM (%)	Relapse (%)	Overall survival (%)
Liu et al. (2013) [51]	212	3–18	NR = 24 CR = 188	AraC/BU/CY Semustin/ATG	2.5	1.88	Multiagent	100%	48.8%	40.1%	<2008: 16.8% >2008: 12.2%	<2008: 28.3% >2008: 17.5%	<2008: 61.1% >2008: 74.5%
Sawada et al. (2014) [65]	9 (15)	2–17	Ref./Rel.: 7 CR = 2	FLU/MEL	NA	NA	PTCY based	80%	55.6%	NA	28.5%	57.1%	Ref./Rel.: 14.2% CR = 100%
Jaiswal et al. (2016) [66, 67]	20	2–20	AML Rel./Ref.: 13 ALL CR: 7	FLU/BU/MEL	7.5	6.85	PTCY based	100%	35%	5%	20%	25.7%	64.3%

AL: acute leukemia; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; ATG: antithymocyte globulin; BU: Busulfan; CR: complete remission; CY: cyclophosphamide; GVHD: graft-versus-host disease; FLU: Fludarabine; MA: myeloablative conditioning; Mel.: Melphalan; NR: not in remission; NRM: nonrelapse mortality; Ref.: refractory; Rel.: relapsed; TBI: total body irradiation; TT: thiotepa.

Jaiswal SR, Chakrabarti S. Advances in Hematology 2016

Sources of stem cells

	Advantages	Disadvantages
BM	- adequate HSC content - low T cell content	- collect in OR, under GA
PB	- adequate HSC - rapid hematopoietic recovery	- use growth factor - high T cell content - only adequate wt. donor
CB	- naive HSC (immature) - very low T cell content - low transmission of viral infection	- low SC content - one-time collection only - delay hematopoietic recovery

Indications for HSCT in ALL

1. High-risk in 1st complete remission (CR1), defined as:

- Infants with MLL (myeloid/lymphoid or mixed lineage leukemia) rearrangements < 6 months of age with high risk characteristics, or
- Severe hypodiploidy (< 44 chromosomes and/or a DNA index of < 0.81), or
- M3 bone marrow at end of induction, or
- M2 bone marrow at end of induction with M2-3 at Day 42

LANZKOWSKY'S MANUAL OF PEDIATRIC HEMATOLOGY AND ONCOLOGY, 2016

Indications for HSCT in ALL

2. High-risk CR2, defined as:

- Ph +ve ALL or
- Bone marrow relapse < 36 months from induction or
- T-lineage relapse at any time or
- Early isolated CNS relapse (<18 months from diagnosis) or
- Slow re-induction (M2-3 bone marrow at Day 28) after relapse at any time

3. Any 3rd or subsequent CR

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Indications for HSCT in AML

- High-risk patient in CR1
  - Preceding MDS
  - High risk cytogenetics: del (5q), -5, -7, abn (3q), t(6;9), complex karyotype (≥ 5 abnormalities)
  - Requiring > 1 cycle of chemotherapy to obtain CR (includes any clinical or radiographic evidence of progressive extramedullary AML)
  - FAB M6 (Acute erythroblastic leukemia)
  - Presence of high (>0.4) allelic ratio FLT3-ITD
  - Therapy-related AML
- Patient in 2nd or greater CR

Disease status at HSCT is a significant predictor of recurrence and OS.

Indications for HSCT in other leukemia

Chronic Myelogenous Leukemia Ph +ve (CML)

1. Chronic unstable phase

2. Early accelerated phase or

3. Chronic phase after treatment for blast crisis

Juvenile Chronic Myeloid Leukemia (JCML)

Juvenile Myelo-Monocytic Leukemia (JMML)

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1. Acute myeloid leukemia in remission
2. Acute Lymphoblastic Leukemia (ALL)
   - CR1: Philadelphia chromosome, T cell with initial WBC >100,000/cumm, Hypodiploidy chromosome, Induction failure, Infant ALL with age < 6 months or initial WBC > 300,000/cumm to intermediate and high risk infant ALL
   - CR2
3. Chronic myeloid leukemia in all stages

Phases in the HSCT

An appropriate donor has been identified.

1. Conditioning phase: approximately 1 week

- Eradication of leukemic cells and create space for new HSC: busulfan, total body irradiation (for ALL)
- Suppression of the immune system to prevent graft rejection: cyclophosphamide, fludarabine

2. Transplant phase: HSC infusion

3. Neutropenic phase: typically lasts 2–4 weeks, significant impaired immune function

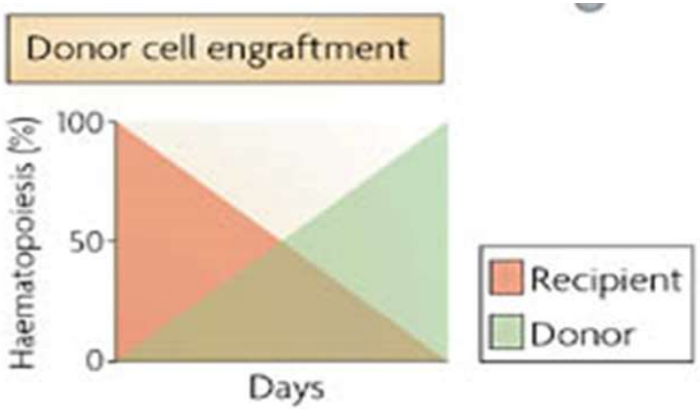
Phases in the HSCT

4. Engraftment phase:

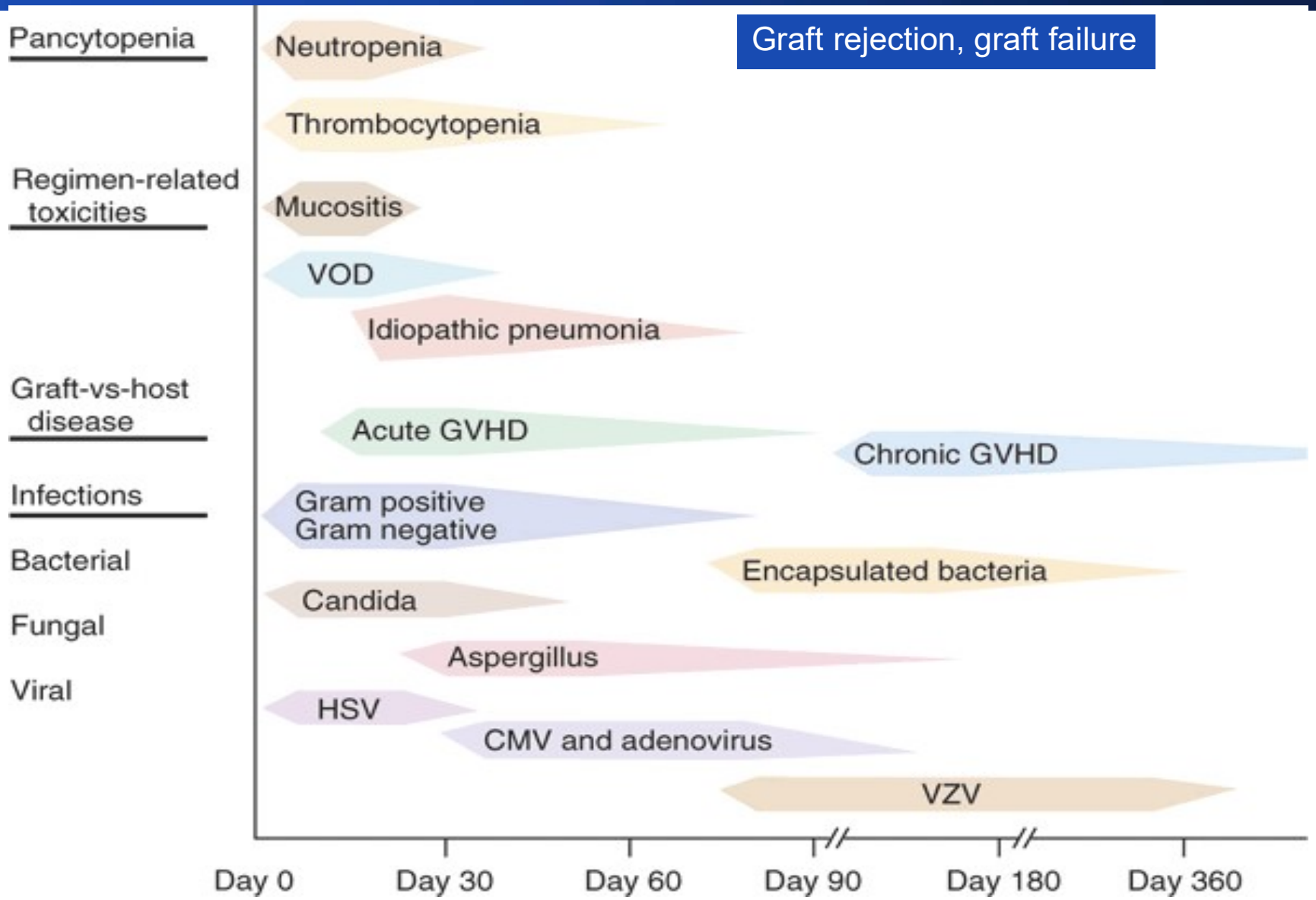
- Healing of the damaged mucosa
- Resolution of infections
- Time for development of acute GVHD
- Delayed process of immune reconstitution due to immunosuppressive medications to prevent GVHD
  1. Corticosteroids: prednisolone, methylprednisolone
  2. T-cell signaling blockade: CSA, FK506
  3. Antiproliferatives: MTX, MMF

5. Postengraftment phase:

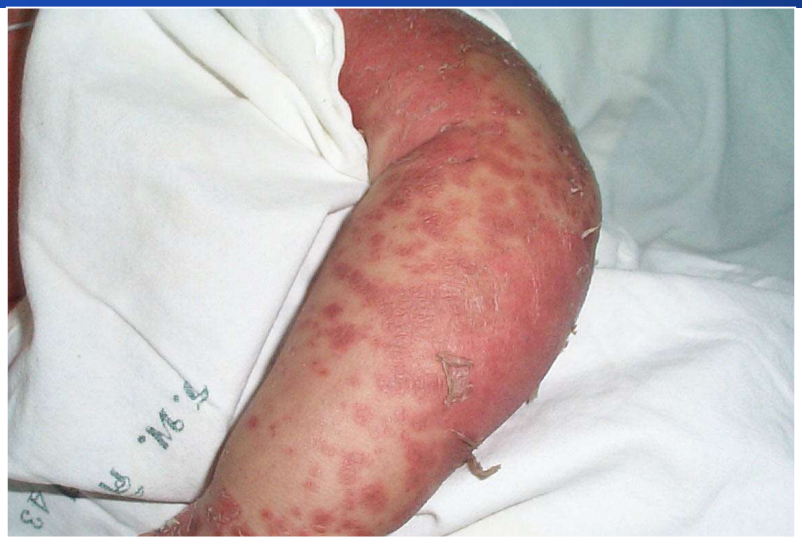
- Recovery of immune reconstitution
- Graft tolerance occurs

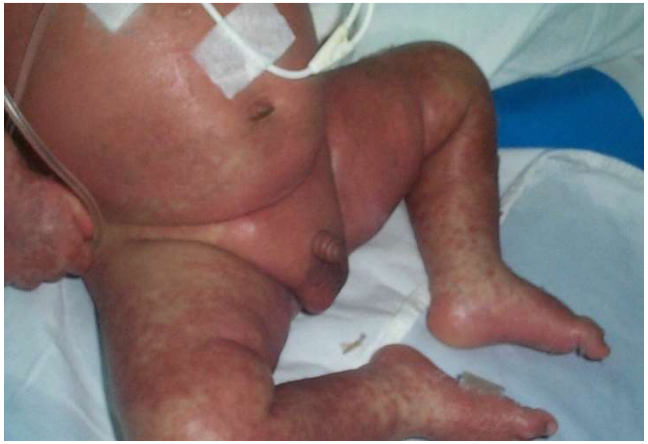


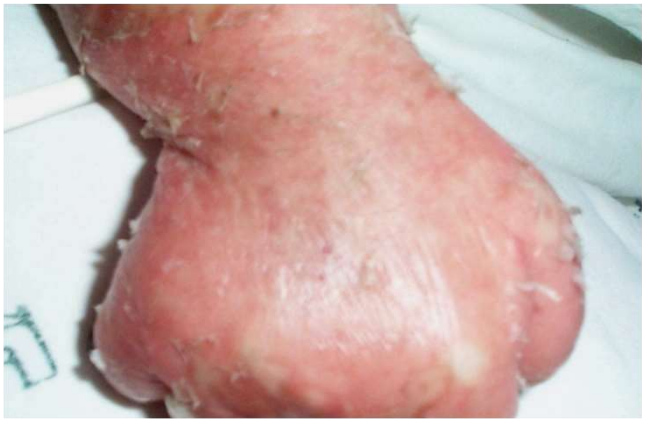
Complications post HSCT

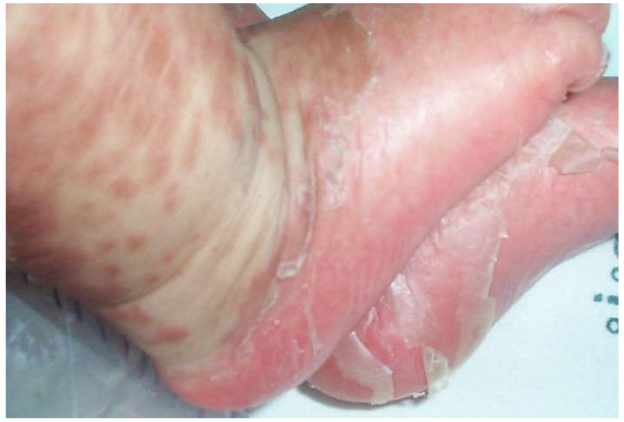


Acute GVHD grade IV

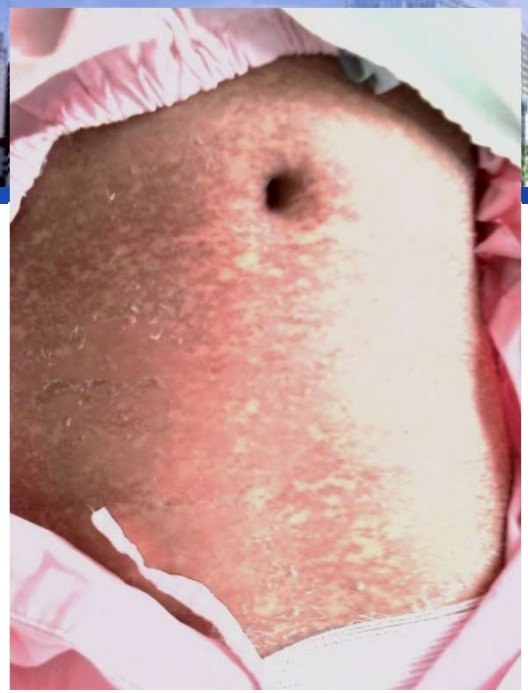


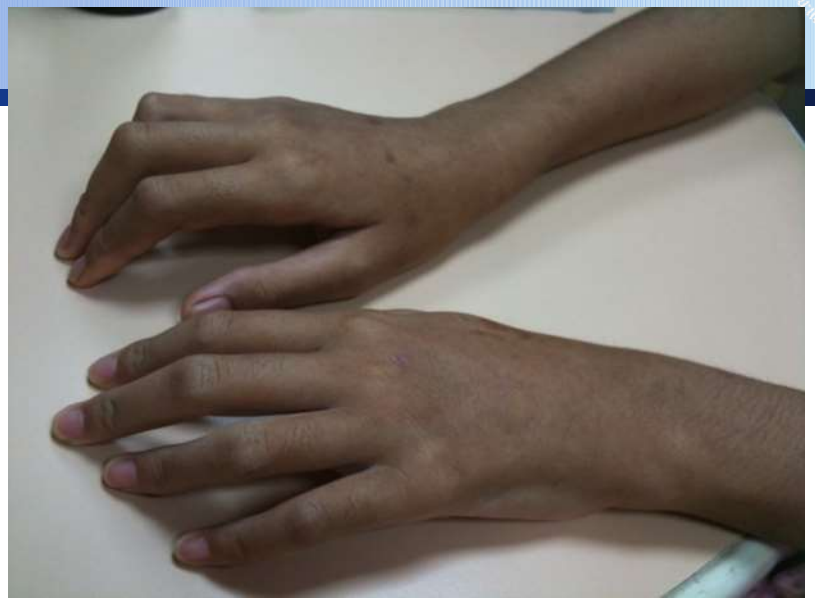


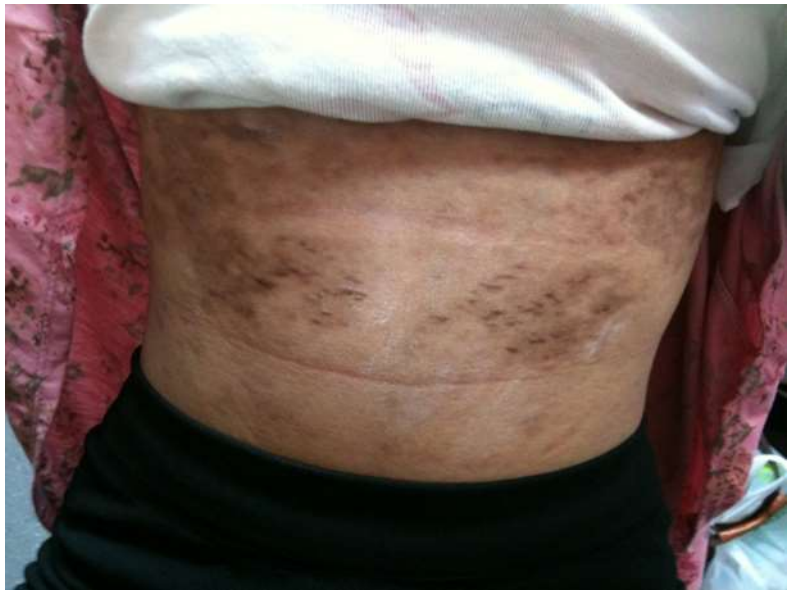


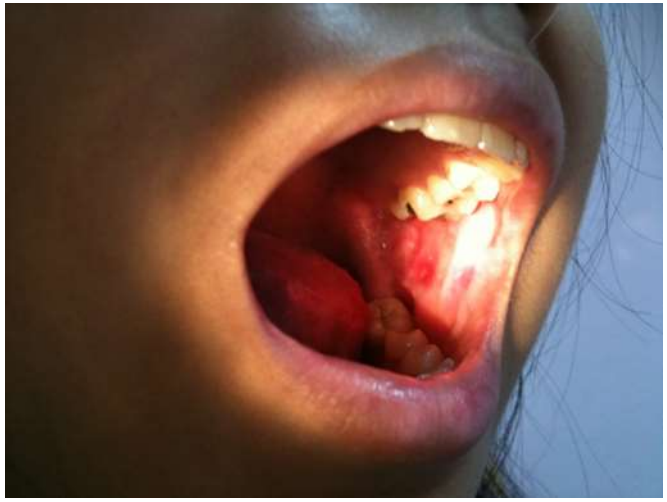


Chronic GVHD

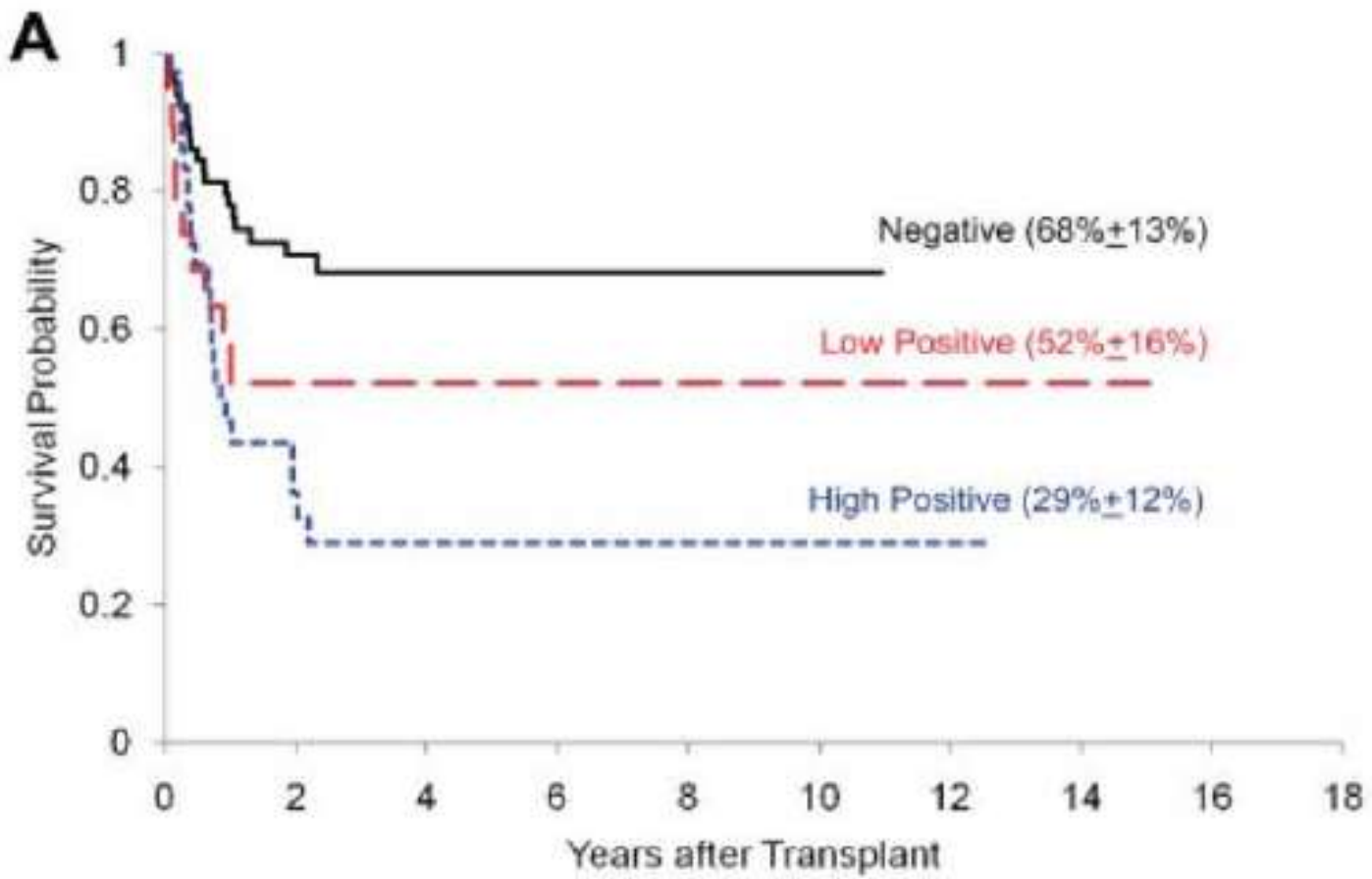






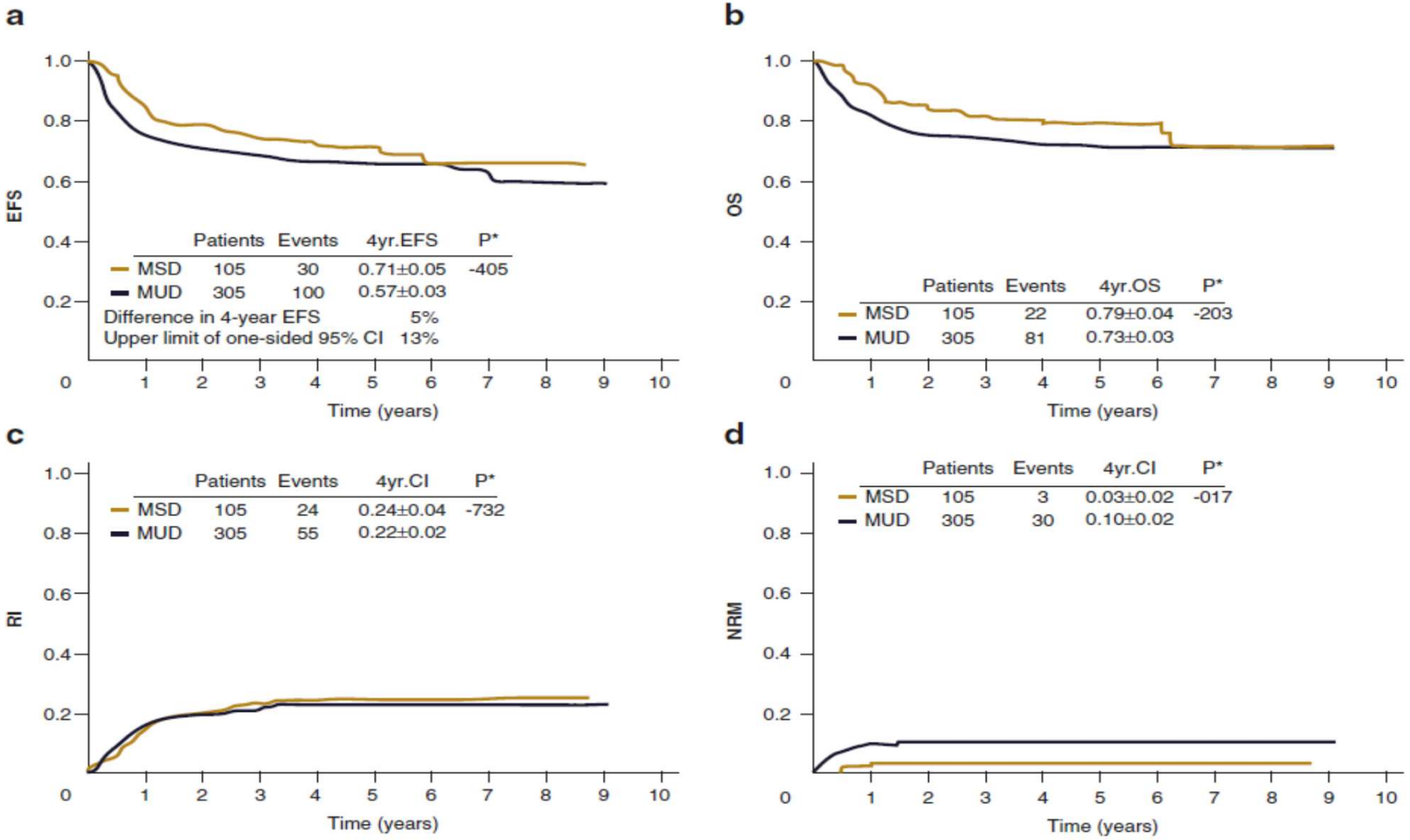


Impact of pre-SCT MRD on Survival after SCT



Leung et al BLOOD 2012

❖ Prospective international multicenter study: ALL-SCT-BFM-2003 trial



Peters et al. 2015

Factors that influence outcome of HSCT

- Remission status of leukemia
- Type of HSCT
- Dedree of HLA matched
- Sources and cell doses of viable HSC
- Conditioning regimen
- Pre-HSCT condition of the patient: organ dysfunction
- Supportive care post-HSCT

Role of targeted therapy in HSCT

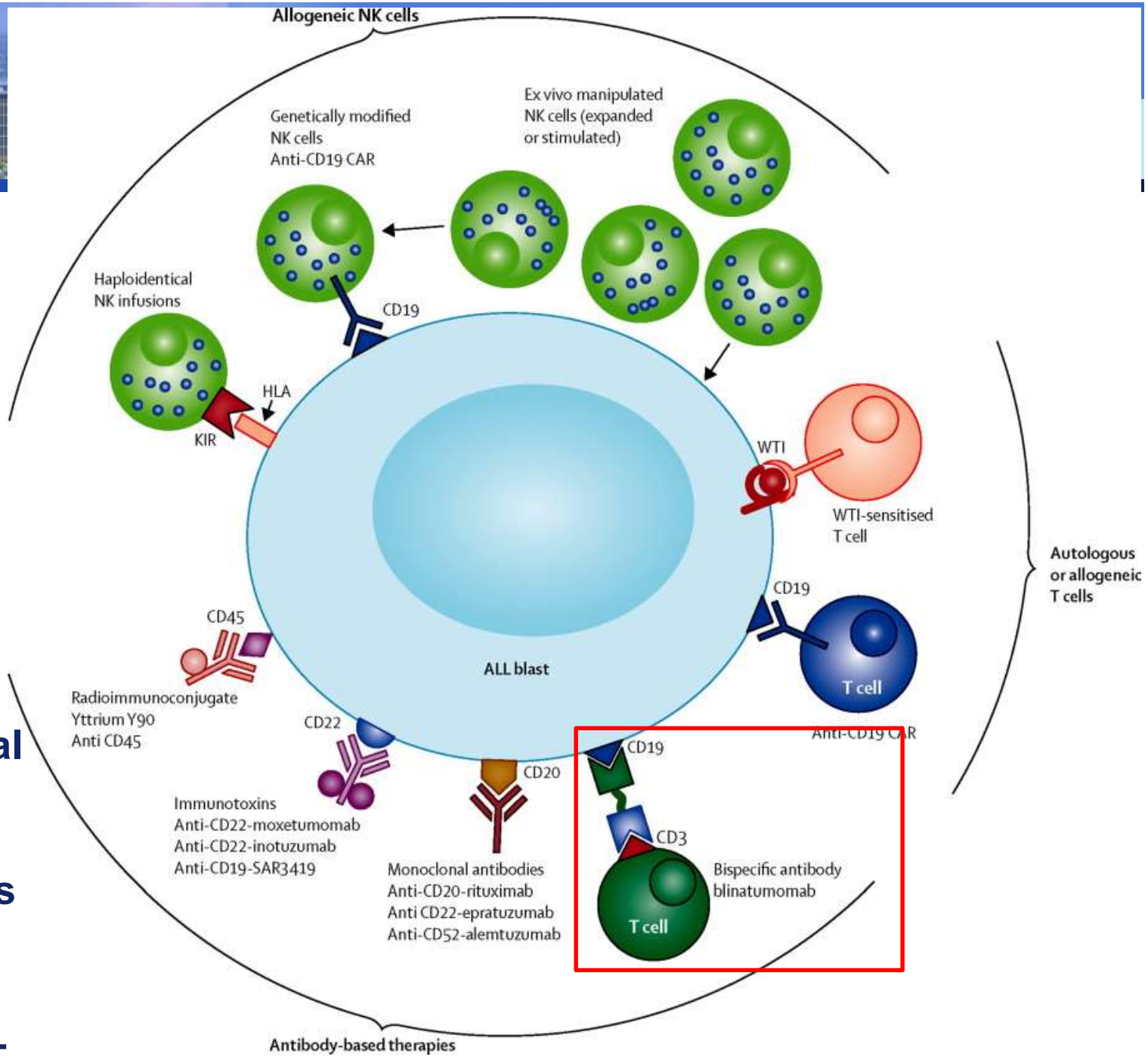
- Specific-antibody to leukemic cell
- Immunotherapy: CART cell, NK cell

- Pre-HSCT: induce molecular remission
- Post-HSCT: reduce relapse rate

- Immunotherapy: donor lymphocyte infusion (DLI)

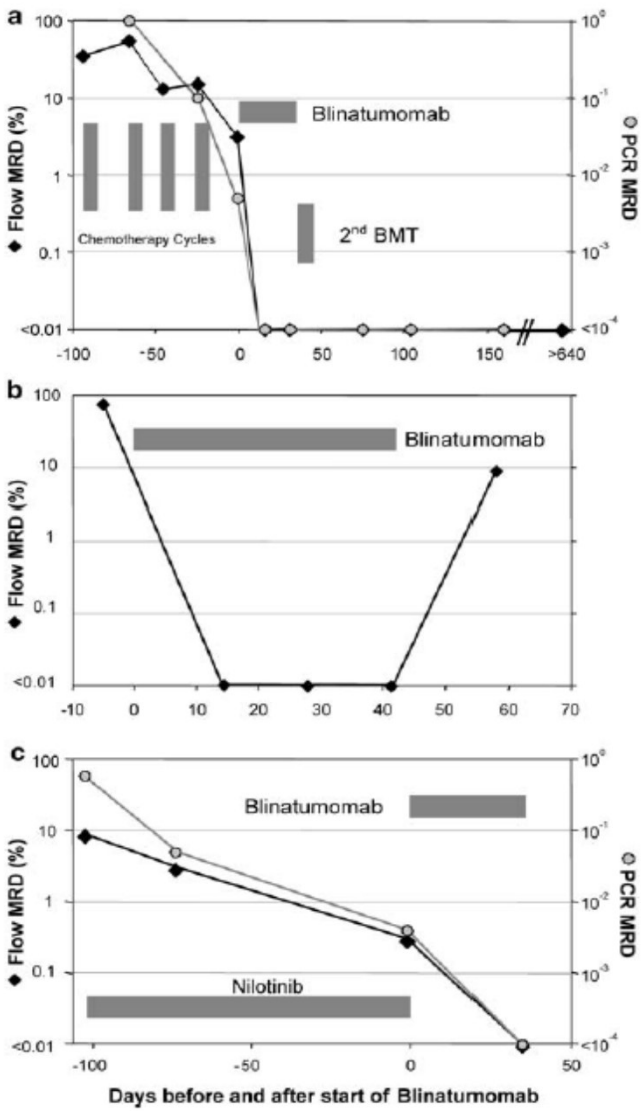
- Post-HSCT: enhance donor engraftment in mixed chimerism and induce remission in relapsed post-HSCT patients.

Immunological approaches under investigations for childhood relapsed ALL



Lancet. 2013

Complete remission after blinatumomab-induced donor T-cell activation in three pediatric patients with post-transplant relapsed acute lymphoblastic leukemia



This first clinical experience in three pediatric patients with B-precursor ALL showed that blinatumomab was well tolerated and rapidly induced MRD-negative CRs in refractory B-precursor ALL after multiple relapses and allogeneic HSCT. It is noteworthy that none of the patients showed any signs of graft-versus-host disease despite the engagement of donor-derived HLA-matched, partially matched or three-loci mismatched haploidentical T lymphocytes. These promising findings warrant clinical trials in pediatric patients with relapsed/refractory B-precursor ALL before and after allogeneic HSCT.

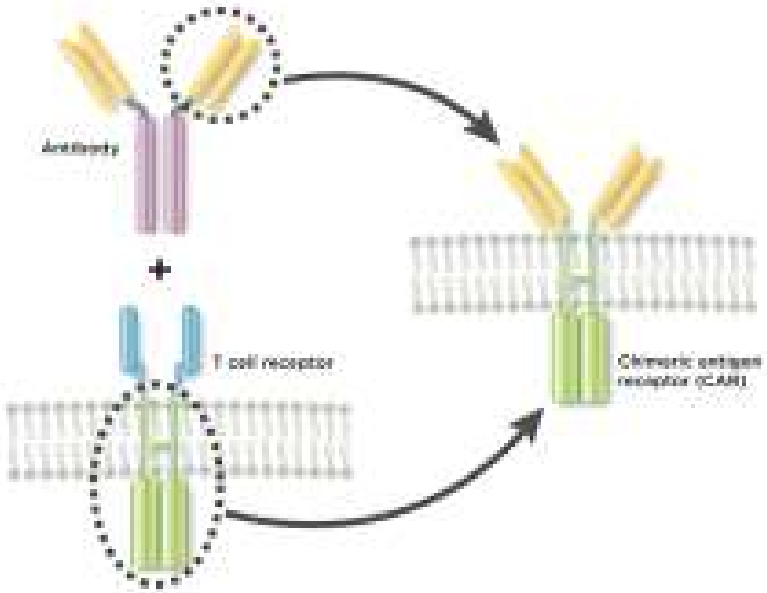
Leukemia (2011) **25,** 181–184; doi:10.1038/leu.2010.239;

First Author and Reference	Program CAR	Population	Response	CRS	Neurologic Toxicity
		ALL			
Maude [4]	PENN 4-1BB	n = 30 (r/rALL) Pediatrics and adults	CR = 90%	100% CRS 27% severe	43% total
Maude [5]	Novartis Multicenter 4-1BB	n = 75 Pediatrics and AYA	CR = 81% MRDNeg = 81%	77% total	13% grade 3
Park [7]	MSKCC CD28	n = 53 Adults	CR = 83% MRDNeg = 67%	85% total 26% severe (1 grade 5)	42% grades 3-4
Lee [3]	NCI CD28	n = 21 Pediatrics and AYA	CR = 67%	76% CRS 28% severe	29% total
Turtle [10]	Seattle 4-1BB	n = 30 Adults	CR = 93%	83% CRS	50% severe
Gardner [1]	Seattle 4-1BB	Pediatrics and AYA n = 45	CR = 93% MRDNeg = 93%	93% CRS 23% severe	49% total 21% grades 3-4
NHL and CLL					
Schuster [9]	PENN 4-1BB	n = 28 (DLBCL/FL)	CR = 57%	57% CRS 18% severe	11% severe
Schuster [12]	Novartis Multicenter 4-1BB	n = 93 (DLBCL)	CR = 40%	58% CRS 9% severe	12% ≥ grade 3
Neelapu [6]	KITE Multicenter CD-28	n = 111 (DLBCL /TFL/PMBCL)	CR = 54%	93% CRS 13% severe	28% ≥ grade 3
Abramson [11]	Juno Multicenter 4-1BB	n = 91 (DLBCL/FL/PMBCL/MCL)	CR = 46%	35% CRS 1% severe	Total 35% 12% ≥ grade 3
Kochenderfer [2]	NCI CD28	n = 15 (NHL/CLL)	CR = 53% PR = 27%	27% severe	40% total
Porter [8]	PENN 4-1BB	n = 14 (CLL)	CR = 29% PR = 29%	64% total 28% severe	43% total 1/14 grade 4

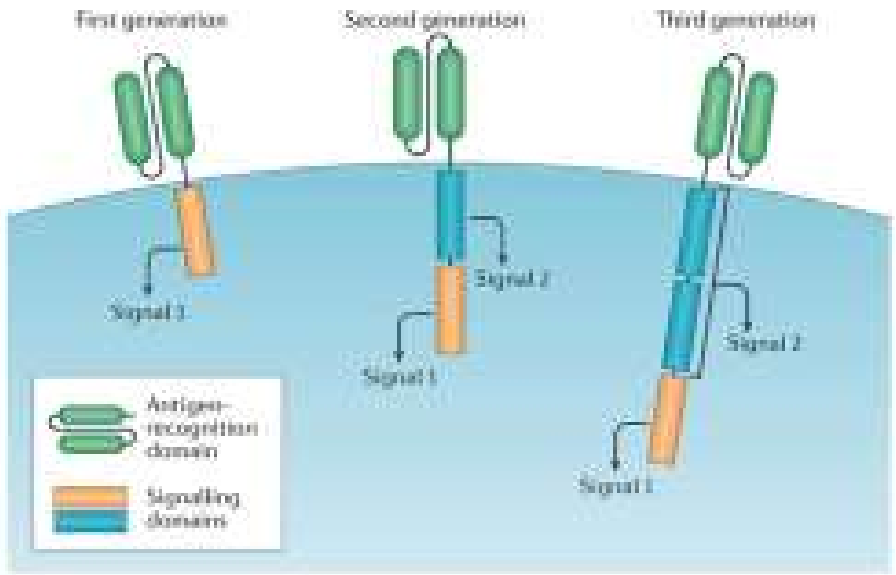
chimeric antigen receptor (CAR) – modified T-cell lymphocytes against CD19 antigen

N. Frey, D. Porter / Biol Blood Marrow Transplant 25 (2019) e123-e127

- A phase II single arm multicenter trial to determine the efficacy and safety of chimeric antigen receptor (CAR) – modified T-cell lymphocytes against CD19 antigen in pediatric patients with relapsed/refractory B-cell ALL
- Multicenter: Siriraj hospital and Ramathibodi hospital



A chimeric antigen receptor, or CAR, joins together part of an antibody and part of a T cell receptor.



Nature Reviews | Clinical Oncology

Summary

- HSCT increase chance of curative Rx for childhood leukemia especially in high-risk and relapsed disease.
- Significant morbidity and mortality → Pretransplant counselling is important.
- Advance in leukemic targeted Rx combine with HSCT and improvements in supportive care → contribute to better outcome in HSCT

Thank you for your attention